Simultaneous EEG-fMRI Study of Audiovisual Sensory Processing

by

Nasim Shams

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Department of Medical Biophysics
University of Toronto

© Copyright by Nasim Shams. 2017
Simultaneous EEG-fMRI Study of Audiovisual Sensory Processing

Nasim Shams

Doctor of Philosophy

Department of Medical Biophysics
University of Toronto

2017

Abstract

Simultaneous acquisition of Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) enables studying of brain function with high spatial resolution of fMRI and high temporal resolution of EEG. The complementary characteristics of the two modalities have made simultaneous EEG-fMRI into a rapidly growing neuroimaging technique with a wide range of cognitive and clinical applications. This thesis uses simultaneous EEG-fMRI to investigate the relationship between electrophysiological activity of the brain and the corresponding hemodynamic response during sensory processing of auditory and visual stimuli.

Despite major improvements during the short history of EEG-fMRI, several technical and methodological challenges still remain. The main challenge in EEG-fMRI is the compromised EEG data quality. EEG data recorded inside the MR scanner is contaminated by artifacts caused by the MR magnetic fields. This thesis provides a comparative evaluation of the existing EEG artifact removal methods and proposes new analysis approaches to improve the EEG data quality.

Another open question in the field of EEG-fMRI is the optimal choice of measures and techniques for data integration. This thesis proposes a new multivariate approach for EEG-fMRI data integration, which enables taking advantage of the full spectrum of the data available in two
modalities. The proposed multivariate technique as well as conventional univariate methods are then used to explore the relationship between various aspects of the brain’s electrophysiological activity (i.e. the transient evoked activity, oscillatory evoked activity and spontaneous oscillatory activity) and the associated hemodynamic response in auditory and visual cortices.
Dedications

To

Ahmad,

Nasrin & Behrouz,

Amir & Antonella.
Acknowledgments

I would like to thank my supervisor Dr. Stephen Strother for his help, support and guidance throughout my PhD studies; He has been a great mentor over the years. I am very grateful for the freedom that I was given to explore various research areas and encouragement and support that I received for participating in various workshops, conferences and scientific meeting during my PhD studies which enriched my knowledge and helped me better understand the field and also be exposed to novel ideas.

I am also grateful to advisory committee members Dr. Claude Alain, Dr. Simon Graham and Dr. Anne Martel for their guidance, support, probing questions and suggestions during committee meetings and their help in my research in the past years. The guidance that I received from them as well as my advisor paved the way for completion of my graduate studies.

I would also like to thank all my colleagues who assisted me through different stages of this work. Specifically I would like to acknowledge assistance from:

Dr. Babak Afshin-pour for providing the initial PLS Matlab code.

Mr. Filomeno Cortese for assisting me with preparing the presentation software code for stimulus delivery, as well as helping with subject preparation during the scan sessions.

Abiramy Uthirakumaran and Nesha Mathikcanta for assisting me with recruitment and preparation of participants in the last phase of data collection.
# Table of Contents

Dedications .................................................................................................................................................. iv
Acknowledgments ......................................................................................................................................... v
Table of Acronyms ...................................................................................................................................... ix
List of Tables ............................................................................................................................................... xi
List of Figures ............................................................................................................................................. xii

## Chapter 1: Introduction

1.1 Electroencephalography (EEG) ........................................................................................................... 1
  1.1.1 EEG Oscillations .......................................................................................................................... 3
  1.1.2 Event-related potentials (ERPs) .................................................................................................... 5
1.2 Functional Magnetic Resonance Imaging (fMRI) .................................................................................. 8
1.3 EEG-fMRI ............................................................................................................................................. 12
  1.3.1 Motivation: .................................................................................................................................. 12
  1.3.2 Integration strategies ................................................................................................................... 13
  1.3.3 Technical considerations and challenges ................................................................................... 15
1.4 Applications of EEG-fMRI .................................................................................................................. 17
  1.4.1 EEG-fMRI to Study the Evoked Response of the Brain ............................................................. 18
  1.4.2 Oscillatory/Spontaneous activity ................................................................................................. 23
  1.4.3 Epilepsy ...................................................................................................................................... 26
1.5 Summary ............................................................................................................................................... 28

## Chapter 2: EEG Analysis Methods and Artifact Removal for Simultaneous EEG-fMRI

2.1 Introduction ......................................................................................................................................... 33
2.2 Materials and Methods ...................................................................................................................... 36
  2.2.1 Participants .................................................................................................................................. 36
  2.2.2 Stimuli and procedure ................................................................................................................ 36
  2.2.3 Data acquisition .......................................................................................................................... 37
  2.2.4 MR gradient artifact removal ...................................................................................................... 39
  2.2.5 BCG artifact removal .................................................................................................................. 40
  2.2.6 Optimization of the artifact removal pipeline ............................................................................ 41
  2.2.7 EEG data processing .................................................................................................................. 42
  2.2.8 Evaluation criteria ..................................................................................................................... 42
Chapter 2 : Univariate Analysis of Evoked BOLD and EEG Responses .............................................. 66
3.1 Introduction .................................................................................................................................. 66
3.2 Methods ......................................................................................................................................... 68
  3.2.1 FMRI preprocessing .................................................................................................................... 69
  3.2.2 GLM Data Analysis ................................................................................................................... 72
  3.2.3 Experiment design ..................................................................................................................... 74
  3.2.4 Single-trial fMRI response estimation ....................................................................................... 76
  3.2.5 Free surfer and ROI generation ............................................................................................... 77
  3.2.6 Robust regression .................................................................................................................... 78
  3.2.7 Analysis of EEG data .............................................................................................................. 79
  3.2.8 Feature evaluation and regression analysis .............................................................................. 80
3.3 Results ........................................................................................................................................... 82
3.4 Discussion ........................................................................................................................................ 95

Chapter 4 : A Multivariate Approach to Analysis of Simultaneously Recorded Evoked EEG and BOLD fMRI Responses .................................................................................................................................................. 99
4.1 Introduction ...................................................................................................................................... 99
4.2 Methods .......................................................................................................................................... 103
  4.2.1 Data integration and analysis ................................................................................................... 104
4.3 Results ............................................................................................................................................ 110
4.4 Discussion ....................................................................................................................................... 116
  4.4.1 Visual results .......................................................................................................................... 116
  4.4.2 Auditory results ...................................................................................................................... 117
  4.4.3 Potential extensions and applications of the proposed model ............................................. 118

Chapter 5 : Task-Related BOLD Signal and EEG Oscillations in the Sensory Cortices ................................................................................................................................................................................. 119
5.1 Introduction .................................................................................................................................... 119
5.2 Methods .......................................................................................................................................... 121
5.3 Results ............................................................................................................................................ 126
5.4 Discussion ....................................................................................................................................... 133
Chapter 6 : Conclusions and Future Directions ................................................................. 136
Thesis publications ........................................................................................................ 148
References ..................................................................................................................... 149
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>adaptive noise cancellation (ANC)</td>
<td>40</td>
</tr>
<tr>
<td>analysis of variance (ANOVA)</td>
<td>55</td>
</tr>
<tr>
<td>auditory evoked potentials (AEPs)</td>
<td>21</td>
</tr>
<tr>
<td>average artifact subtraction (AAS)</td>
<td>34</td>
</tr>
<tr>
<td>ballistocardiogram (BCG)</td>
<td>16</td>
</tr>
<tr>
<td>blood oxygenated level-dependent (BOLD)</td>
<td>4</td>
</tr>
<tr>
<td>Canonical Correlation Analysis (CCA)</td>
<td>15</td>
</tr>
<tr>
<td>cerebral blood flow (CBF)</td>
<td>9</td>
</tr>
<tr>
<td>critical difference (CD)</td>
<td>55</td>
</tr>
<tr>
<td>Echo planar imaging (EPI)</td>
<td>10</td>
</tr>
<tr>
<td>electrocardiogram (ECG)</td>
<td>37</td>
</tr>
<tr>
<td>Electroencephalography (EEG)</td>
<td>1</td>
</tr>
<tr>
<td>event-related desynchronization (ERD)</td>
<td>99</td>
</tr>
<tr>
<td>event-related potential (ERP)</td>
<td>2</td>
</tr>
<tr>
<td>event-related synchronization (ERS)</td>
<td>99</td>
</tr>
<tr>
<td>evoked potential (EP)</td>
<td>2</td>
</tr>
<tr>
<td>field of view (FOV)</td>
<td>37</td>
</tr>
<tr>
<td>functional magnetic resonance imaging (fMRI)</td>
<td>1</td>
</tr>
<tr>
<td>general linear model (GLM)</td>
<td>14</td>
</tr>
<tr>
<td>hemodynamic response function (HRF)</td>
<td>10</td>
</tr>
<tr>
<td>Independent Component Analysis (ICA)</td>
<td>15</td>
</tr>
<tr>
<td>inter stimulus interval (ISI)</td>
<td>36</td>
</tr>
<tr>
<td>Least Square-Separate (LSS)</td>
<td>76</td>
</tr>
<tr>
<td>local autoregressive average (LAURA)</td>
<td>7</td>
</tr>
<tr>
<td>local field potentials (LFP)</td>
<td>11</td>
</tr>
<tr>
<td>local field potentials (LFPs)</td>
<td>2</td>
</tr>
<tr>
<td>low resolution electromagnetic tomography (LORETA)</td>
<td>7</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>8</td>
</tr>
<tr>
<td>mismatch negativity (MMN)</td>
<td>21</td>
</tr>
<tr>
<td>multiunit action potentials (MUA)</td>
<td>11</td>
</tr>
<tr>
<td>optimal basis selection (OBS)</td>
<td>34</td>
</tr>
</tbody>
</table>
partial least squares (PLS) .......................................................................................................................... 31
positron emission topography (PET) .................................................................................................................. 12
principal component analysis (PCA) ................................................................................................................ 29
radio frequency (RF) ....................................................................................................................................... 8
region of interest (ROI) .................................................................................................................................. 77
signal to noise ratio (SNR) ................................................................................................................................ 5
single unit action potentials (SUA) ................................................................................................................... 12
singular value decomposition (SVD) ................................................................................................................. 106
sound pressure level (SPL) ............................................................................................................................... 37
the left lateral prefrontal cortex (LPFC) ........................................................................................................... 144
trimmed standard deviation (TSTD) ................................................................................................................ 79
visual evoked potentials (VEPs) ....................................................................................................................... 16
List of Tables

**Table 2.1:** Performance comparison for the peak detection methods implemented in Analyzer-II and EEGLab. .................................................................................................................................. 49

**Table 2.2:** Mean SNR difference values (column – row) of pipelines from Analyzer-II, EEGLab with three versions of optimal basis selection (OBS: 3PC, fix Opt, Ind Opt), and outside scanner recording (No MR). The upper half of the table (blue shade) shows mean SNR differences for visual evoked potentials and the lower half (purple shade) shows mean SNR differences for auditory evoked potentials. The statistical significance of each value is indicated as *p<0.005, **p<0.001, ***p<0.0001. ............................................................................................................. 52

**Table 2.3:** Mean SNR difference values (column – row) of the four pipelines composed by combining MR gradient and BCG correction methods of different packages compared with SNRs recorded outside the scanner. For the EEGLab package, the individually optimized method was selected as the BCG algorithm. The upper half of the table (blue shade) shows mean SNR differences for visual evoked potentials and the lower half (purple shade) shows mean SNR differences for auditory evoked potentials. The statistical significance of each value is indicated as *p<0.005, **p<0.001, ***p<0.0001 .......................................................... 54

**Table 2.4:** Results for task detection using contralateral and ipsilateral P1 amplitude difference.59

**Table 3.1:** Robust regression summary for visual ERP components in the full ROI and individual ROIs. The statistical significance of the slopes are indicated as *p<0.05, **p<0.01, ***p<0.001. .................................................................................................................................. 91

**Table 3.2:** Robust regression summary for auditory ERP components in the full ROI and individual ROIs. The statistical significance of the slopes are indicated as *p<0.05, **p<0.01, ***p<0.001. .................................................................................................................................. 92
# List of Figures

**Figure 1.1**: A schematic of changes in the blood flow and oxygenation level during a) rest and b) neural activity. In response to the increased oxygen demand caused by neural activity, the local vessels dilate and increase the blood flow to regions of neural activity. The increase of blood flow leads to changes of oxygenated and deoxygenated hemoglobin. The time scale of changes in relative concentration of oxygenated and deoxygenated hemoglobin following neural activity is illustrated in panel c. Source (a,b:https://www.ndcn.ox.ac.uk/. c: redrawn from (Huettel,2009))

**Figure 1.2**: Comparison of EEG data recorded inside and outside the scanner; (a) normal EEG data recorded outside the scanner in normal EEG recording environment, (b) EEG data recorded inside the scanner with the participant lying inside the scanner bore (no image acquisition). The distortion in the data is caused by the BCG artifact alone (c) EEG data recorded inside the scanner during MR image acquisition. The high amplitude of MR artifacts makes the EEG data indistinguishable.

**Figure 1.3**: A schematic of an event-related potential in response to visual stimulation recorded from the occipital electrode site. (adapted from (Woodman et al. 2010))

**Figure 1.4**: A schematic of an event-related potential in response to auditory stimulation recorded from a central electrode site (i.e. Cz). The earliest waves in the first 10 ms (I - VI) are generated in the auditory brainstem pathways, components at the latency of approximately 10-50 ms are called mid-latency components, which are mostly generated in the thalamo-cortical pathway. Subsequent negative and positive waves (P1, N1, P2, N2, P3) are generated in different sub regions of primary and secondary auditory cortex. Note the logarithmic time scale (adapted from (Woodman et al. 2010)).

**Figure 2.1**: Block diagram of basic EEG processing steps.

**Figure 2.2**: Group averaged left/right auditory and visual evoked potentials. Each evoked potential is calculated by averaging signal from a cluster of electrodes as indicated in the picture.

**Figure 2.3**: Sample peak regressors for auditory evoked potentials. The figure shows peak templates and their corresponding derivatives used in the linear regression model.
**Figure 2.4**: Visual and auditory evoked potentials for two sample participants. Each column includes ERPs obtained from one run and rows represent different stimulus conditions. The red waveforms represent ERPs achieved by AnalyzerII processing pipeline and the blue waveforms represent EEGlab results with optimization.

**Figure 2.5**: Optimal number of PCs in the OBS algorithm for fix (green line) vs individually (yellow box plots) optimized pipelines. The box-bar plots illustrate the range of optimal PC number (nPC) across different runs and participants for each condition. The green dash to the left shows the nPC selected by the fix optimization process for comparison.

**Figure 2.6**: Effect of using the adaptive noise cancellation (ANC) filter in EEGlab on the SNR and nPC. Including the ANC in the pipeline resulted in a slight increase in the SNR but no significant effect on the nPC was observed.

**Figure 2.7**: Comparison of SNR values for auditory and visual evoked potentials obtained with different correction algorithms. The outside scanner measurement results (no MR) are also provided for comparison. Error bars indicate the standard error of the mean (SEM).

**Figure 2.8**: Comparison of SNR values for pipelines generated by combining correction algorithms from Analyzer and EEGlab. The pipelines include: 1) Analyzer-II—both MR correction and BCG correction are performed in algorithms provided in Analyzer-II, 2) EEGlab(MR)+Analyzer-II(BCG)—MR correction performed in EEGlab followed by BCG correction in Analyzer-II, 3) Analyzer(MR)+EEGlab(BCG)—MR correction performed in Analyzer-II followed by individually optimized BCG correction in EEGlab, 4) EEGlab ind—both correction steps were performed in EEGlab with optimized parameters, 5) noMR—dataset recorded outside the scanner.

**Figure 2.9**: Critical difference (CD) diagram for methods illustrated in Figure 2.6, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the best mean SNR performance. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.

**Figure 2.10**: Critical difference (CD) diagram for methods illustrated in Figure 6, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the best mean SNR performance. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.
Figure 2.11: Single trial variability of the peak-to-peak amplitude for different tasks and pipelines.

Figure 2.12: Critical difference (CD) diagram for methods illustrated in Figure 2.10, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 single trial peak-to-peak variability measures. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.

Figure 2.13: Schimmel’s measure for different EEG processing pipelines across four stimulus conditions.

Figure 2.14: Critical difference (CD) diagram for methods illustrated in Figure 2.12, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the Schimmel’s noise measure. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.

Figure 3.1: Block diagram of fMRI processing pipeline.

Figure 3.2: Visual and Auditory ROIs for a sample participant: a) Auditory ROIs. b) Visual ROIs from the left and right view. The inflated brain surfaces are created using SUMA software packages.

Figure 3.3: fMRI activation maps for a sample participant. Each row represents SPMs for a stimulus condition with T-values thresholded at P<0.001 (uncorrected).

Figure 3.4: Regression results for visual (left) and auditory (right) ERP components vs BOLD response in the visual/auditory cortex. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.

Figure 3.5: Regression results for visual P1 in four ROIs of the visual cortex. Each point on the plots represents the visual P1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.

Figure 3.6: Regression results for visual N1 in four ROIs of the visual cortex. Each point on the plots represents the visual N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.7: Regression results for the peak to peak P1-N1 measure in four ROIs of the visual cortex. Each point on the plots represents the visual P1-N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm...

Figure 3.8: Regression results for the auditory P2 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory P2 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm...

Figure 3.9: Regression results for the auditory N1 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm...

Figure 3.10: Regression results for the auditory N1-P2 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory N1-P2 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm...

Figure 3.11: Visual analysis results for sample participants. The horizontal axis represents the averaged single trial BOLD responses (calculated using LSS) for the four bins. The vertical axis represents ERP peak SNR for averaged ERP within each bin. Each panel illustrates the relationship between one ERP peak and the BOLD response. Within each panel, the relationships for individual ROIs are plotted using different colors. The blue curve represents the relationship in area V1, red represents V2 and green represents V3...

Figure 3.12: Auditory analysis results for sample participants. The horizontal axis represents the averaged single trial BOLD responses (calculated using LSS) for the four bins. The vertical axis represents ERP peak SNR for averaged ERP within each bin. Each panel illustrates the relationship between one ERP peak and the BOLD response. Within each panel, the relationships for individual ROIs are plotted using different colors. The blue curve represents the relationship in area A1, red represents A3 and green represents A4...

Figure 4.1: Block diagram of the input data matrices and the leave-one-out PLS framework. a) Structure of the X and Y input matrices for the PLS analysis. Each row of the X matrix contains frequency band values across all electrode channels for one participant. The corresponding row
in the Y matrix contains averaged BOLD response in the four ROIs for the same participant. b) leave-one-out iteration of the PLS analysis. At every iteration data from one participant is excluded from the PLS analysis and later projected on the saliences obtained from the remaining (N-1) participants.

**Figure 4.2:** Visual outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.

**Figure 4.3:** Auditory outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.

**Figure 4.4:** PLS-CV results for the visual response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographic maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of $p<0.05$ (*), or $p<0.001$ (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.

**Figure 4.5:** Stability of the EEG and fMRI saliences for the visual response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.

**Figure 4.6:** PLS-CV results for the auditory response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors.
The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of p<0.05 (*), or p<0.001 (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.

**Figure 4.7:** Stability of the EEG and fMRI saliences for the auditory response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.

**Figure 5.1:** Visual outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.

**Figure 5.2:** Auditory outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.

**Figure 5.3:** PLS-CV results for the visual response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of p<0.5 (*), or p<0.001 (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.

**Figure 5.4:** Stability of the EEG and fMRI saliences for the visual response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.
Figure 5.5: PLS-CV results for the auditory response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrate the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of p<0.5 (*), or p<0.001 (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.

Figure 5.6: Stability of the EEG and fMRI saliences for the auditory response. a) Penetration maps for the EEG auditory components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.

Figure 5.7: PLS-CV results using fMRI motion parameter estimates (roll, pitch, yaw, dS, dL, dP) instead of the BOLD response. Each row represents results with one pair of components and latent variables. The topographic maps on left show the spatial distributions of the EEG oscillatory power that may confounded with motion related BOLD signal. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding motion fMRI salience vectors. The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.

Figure 6.1: Schematic of trial structure and conditions used during the EEG/fMRI recording for the Recent Probe paradigm.

Figure 6.2: Group averaged ERP waveform indicating the proactive interference effect. The waveforms represent averaged ERPs recorded for the Negative Non-recent (in blue) versus Negative Recent (in red) stimulus condition. The waveforms are recorded at the Cz electrode and the difference in peak amplitude at ~200 ms and ~500ms represent proactive interference.

Figure 6.3: Group level fMRI SPMs for the proactive interference effect. The SPMs are t-values thresholded at p<0.001 with a cluster size of 40 voxels.
Figure 6.4: Different approaches to analysis of EEG-BOLD response implemented throughout the chapters. The analysis starts with the conventional time and phase locked ERP analysis and then evolves towards the oscillatory activity of the brain.
Simultaneous EEG-fMRI is the combination of two non-invasive neuroimaging modalities: Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). EEG-fMRI enables concurrent study of brain function with the advantageous spatial resolution of fMRI and the advantageous temporal resolution of EEG. Over the last decade, the application of EEG-fMRI has rapidly grown in different areas of clinical as well as cognitive neuroscience research. Despite all the recent progress, many technical, methodological and scientific questions in the field remain to be clarified and addressed. The initial sections of this chapter cover the background on EEG and fMRI, their origins, measurement and their underlying mechanisms of generation. I will then discuss the motivations and rationale behind combining the two techniques, the potential benefits and applications, as well as integration strategies and technical challenges associated with concurrent EEG-fMRI recording. Next, I will review the current EEG-fMRI literature in different application areas with an emphasis on auditory and visual paradigms and results. Finally, I will discuss shortcomings of the existing EEG-fMRI methodology and some of the inconsistencies in the current literature. This is followed by a description of the subsequent chapters in this thesis, and how they address these shortcomings.

1.1 Electroencephalography (EEG)

Electroencephalography (EEG) is one of the oldest non-invasive neuroimaging methods that has been recognized since 1934, when Mathews and Adrian demonstrated that the oscillatory signal recorded from the occipital area in man, namely the alpha rhythm, was in fact of neural origins and not artifactual (Mulert 2010). The EEG signal is generated by an accumulation of the intrinsic electrical activity of neurons and to a lesser extent, glial cells. The transmembrane current in neurons during activation induces time-varying electromagnetic fields. However, the electric field generated by a single neuron is far too small (0.3-0.9 pA) to be measured by EEG electrodes. Usually, 10,000-100,000 neurons that have similar spatial orientation need to be
activated synchronously to generate an electrical field that is detectable with EEG electrodes applied on the scalp.

Neural activations are divided into two general categories based on their spatial and temporal scales: action potentials and local field potentials (da Silva 2009). The action potentials are generated by the fast depolarization of the neuronal membranes and reflect changes of more than 80mv in 1-2ms in the cell membrane. Theses rapid changes in the membrane potential result in generation of an electrical impulse that propagates along the axons without sustainable loss of amplitude and thus enables fast neural communication. Despite their relatively large amplitude, the action potentials (and electrical activity of the white matter in general) have little to no contribution to the scalp EEG recording. This is in part due to the significantly short duration of the action potential spikes, which makes constructive summation unlikely, as well as rapid drop in their amplitude (<60μV) outside of the 50μm radius from the generation site (Henze et al. 2000, Ullsperger 2010b). The second category of activations, local field potentials (LFPs), involve slower (< 250 Hz) changes in the membrane potential due to synaptic activation. LFPs are generated in the gray matter and show more spatial and temporal summation than the spikes. This is in part due to the geometrical shape and organization of neurons in gray matter. Pyramidal neurons are a specific type of neuron in the gray matter that are aligned with their apical dendrites perpendicular to the cortical surface and are thought to be the generators of the EEG signal due to LFPs. Synchronous synaptic activation over an extended patch of gray matter, consisting of approximately 50,000 active pyramidal neurons, results in coherent electromagnetic fields that can be detected by the EEG electrodes (da Silva 2009).

EEG can be used and analyzed in two main ways. First, EEG signal can be used to study the spontaneous oscillatory activity of the brain. These oscillations occur at multiple frequencies and comprise the most prominent features of the EEG signal. Alternatively, EEG can be utilized to study the neural evoked response to a transient event or stimulus through repeated measurement. The result of such analysis is a transient waveform, also known as an event-related potential (ERP) or evoked potential (EP), which reveals spatiotemporal changes in the scalp potentials following the stimulus. A brief discussion of these two approaches is provided below.
1.1.1 EEG Oscillations

The spectral content of the EEG signal can be divided into dominant frequency bands that characterize different brain states ranging from deep sleep to alert wakefulness. A brief overview of the conventional frequency bands associated with different brain states is provided below. However, it should be noted that oscillations of different frequencies can coexist and interact with each other, resulting in a wide range of brain states (Ullsperger 2010b).

**Delta:** Delta rhythms denote oscillations below 4 Hz. In EEG of healthy adults, delta waves characterize deep stages of sleep (stages 3 and 4) and are typically localized to midline cingulate structures (Murphy et al. 2008). The appearance of delta waves during wakefulness is normal in infants and young children, with amplitude increase as a result of sleep deprivation. In adults however, delta activity during wakefulness is considered an indication of a pathological state.

**Theta:** Theta waves are defined as oscillations in the range of 4-8 Hz. They are more prominent during infancy and childhood but can be observed in EEG of healthy adults especially during drowsiness and sleep. The two main sources of theta activity in adults are thought to be the hippocampus and the dorsal anterior cingulate cortex (Onton, Delorme & Makeig 2005). The former is observed during drowsiness and the sleep state while the latter, dominating the midline frontal electrodes, is associated with cognitive performance in working memory tasks (Klimesch 1999, Mitchell et al. 2008).

**Alpha:** Alpha rhythm oscillations, from 8-12 Hz, were the first EEG oscillations reported by Berger (Berger 1929, Michel, Brandeis 2010). Despite extensive research, the functional role and the underlying neural generators of the alpha rhythm are still debated. The early recordings of alpha rhythms were in relaxed awake animals and humans over the occipital area of the cortex. The prominence of the alpha range frequency during eyes closed (resting state) as well as decreases in alpha activity during eyes opening and mental activity has led to the conclusion that alpha oscillations represent an occipital idling rhythm involved in suppression of sensory inputs. However, recent studies show that alpha oscillations can also occur in the frontal, sensory motor, and supplementary motor area (i.e. the mu rhythm) (Pfurtscheller, Andrew 1999) as well as the primary auditory cortex (i.e. the tau rhythm) (Weisz et al. 2011). Furthermore, the concept of the alpha rhythm as a pure cortical idling phenomenon has been challenged by results from more
recent studies showing a relative increase in alpha power associated with increased working memory load (Jensen et al. 2002, Jokisch, Jensen 2007, Michels et al. 2008).

Investigations of the underlying neural mechanisms of alpha power have identified sources in the thalamic nuclei and cortical areas. The interactions between thalamocortical sources of alpha rhythm vary across cortical regions. While thalamic sources can have a large influence on cortical rhythms, the intracortical connections are responsible for propagation of alpha rhythms across the cortex. Hence the coherence between alpha waves recorded from neighboring cortical sites is greater than thalamocortical coherence (Lopes da Silva 1991, Sigala et al. 2014).

In summary, “there is no single alpha rhythm in the brain” (Michel, Brandeis 2010). The functional significance of alpha rhythms and their neural generators can vary depending on where they are recorded in the brain.

**Beta:** Beta rhythms (12-30 Hz) are generally considered the prominent rhythm of cortical activation in a state of enhanced attention or vigilance (Buzsaki et al. 1988, Buzsáki 2006). Due to the wider range of beta band oscillations compared to the bands mentioned above, beta band oscillation is sometimes divided into sub-bands such as beta1 (12-20Hz) and beta2 (20-30Hz). The most widely studied type of beta activity is the beta oscillations recorded from the sensorimotor cortex. Increased coherence in the beta band oscillation over the sensorimotor region during motor activity is thought to play a role in the suppression of the corticospinal pathways, relating the sensory input to the motor command. Regarding the neural sources of beta-band oscillations, experimental results from intracranial recordings and animal studies suggest that the primary generators of these oscillations are distributed within the cortex (da Silva et al. 1970, Freeman, van Dijk 1987). Furthermore, combined EEG-fMRI resting state studies have found blood oxygenated level-dependent (BOLD) correlates of beta band activity in default mode areas (i.e. the posterior cingulate, precuneus, temporo-parietal and dorsomedial prefrontal cortex) (Laufs et al. 2003b). However, it should be noted that the beta activity recorded from the sensorimotor cortex during motor activity is distinct from resting state beta activity and can have different functional significance and neural generators in the brain (da Silva 2009).
**Gamma:** The Gamma band includes oscillatory activity in the 30-100 Hz range. Gamma band activity is generally considered to reflect a state of high neural excitability and active information processing in cognitive tasks. Intracranial recordings in humans support the role of gamma band activity in working memory performance, with amplitude increases dependent on the task load (Fries, Nicolic 2007). Furthermore, increased coherence in the gamma frequency band over the somatosensory cortex have been found to precede the execution of movement (da Silva 2009).

It has been suggested that synchronous gamma band oscillation across distant areas of the brain serves as a central timing mechanism that allows modulation of synaptic activities in these areas. The synchronous synaptic activity may enable functional aggregation of these areas into a network, with the purpose of global feature processing and perception. However, due to the overlap of the gamma frequency band with artifactual signal sources such as muscle movement, the cortical origin of the gamma activity still needs to be confirmed. *In-vitro* models of the cortex suggest sources of gamma rhythm in layers II and III of the somatosensory cortex.

### 1.1.2 Event-related potentials (ERPs)

Event-related potentials are electrical changes recorded from the brain in association with an external stimulus or an activity initiated within the brain itself (Picton, Lins & Scherg 1995). They have been widely used to examine the timing of distributed brain processes involved in perception and cognition. Typically, the amplitude of a single-trial, evoked potential is in the range of a few microvolts, while the background activity can reach tens of microvolts in healthy adults. The signal to noise ratio (SNR) of an individual evoked response is thus much smaller than one. As a consequence, a particular stimulus is repeated many times in typical ERP experiments and stimulus time-locked segments of the recorded EEG signal are averaged across these repeated trials to enhance the SNR ratio for ERPs of experimental interest. This averaging approach preserves the phase-locked ERP response, which captures the brain response with consistent latency and polarity of the waveform across trials while canceling out random noise. Such stimulus locked ERP amplitude averaging is a very common way of designing and analyzing EEG recordings. However, as it will be discussed later, the phase-locked response is a
partial representation of the brain response and alternative analysis methods can provide a more comprehensive image of the brain response.

The typical ERP waveform exhibits several basic “components”. A component is defined as a positive or negative fluctuation that can be visually identified in an ERP waveform. The naming of ERPs is usually based on the presence of specific components in the recorded waveform. These “peaks” (or amplitude extrema) are typically described in terms of their polarity and peak latency from stimulus onset. For example, P100 is a positive peak occurring with a latency of 100 ms. Another naming system is based on sequential numbering of the peaks (e.g. P1, N1, P2, N2 etc.) (Picton, Lins & Scherg 1995). The ERPs corresponding to various stimuli are thus characterized by the latency and sequence of their peak components. In general, components occurring with latencies less than 100 ms are thought to reflect early sensory processing components, components between 100 and 200 ms are thought to reflect late sensory and early cognitive processes, while those after approximately 250 ms are believed to reflect higher-level cognitive processes (Menon, Crottaz-Herbette 2005).

A major question in EEG data analysis is how to localize the neural generators within the brain that are responsible for a certain distribution of electrical potentials – either oscillatory or transient – recorded at the scalp. This question is in fact an ill-posed problem because an infinite number of source distributions in the brain can generate the same scalp potential map. Thus, the only way to solve this difficult inverse problem is to impose constrains and a priori assumptions about the sources. Early approaches consisted of modeling the sources using a dipole model and posing a limit on the number of sources. The major drawback of this approach is that the number of sources needs to be small and known a priori. More recently, distributed source models have been developed to estimate brain electric activity in each point of a large three-dimensional grid of solution points, using a dipolar source of a given strength and orientation at each grind point (Michel, Brandeis 2010). Since this is an underdetermined inverse problem, additional constraints need to be applied to the model. The most prominent branch of the distributed source model approaches incorporate mathematical assumptions such as the minimum norm assumption, which searches the 3D dipole grid for a solution that has the minimal overall current intensity or power. The widely used algorithms developed in this area include the low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al. 2002) and the local
autoregressive average (LAURA) algorithm (de Peralta Menendez, Rolando Grave et al. 2001). LORETA uses Laplacian-weighted, minimum-norm constraints in addition to the minimum norm assumption, smoothing the solution in the 3D dipole space. Alternatively, the LAURA algorithm uses autoregressive averaging as constraints in combination with the minimum norm assumption.

Although distributed source algorithm results have been shown to be reproducible (Schulz et al. 2008), the low spatial resolution of the results remains an issue. Spatial resolution for source localization methods is defined as the minimum separation at which discreet sources can be distinguished. Adding anatomical functional constraints can improve the localization precision, particularly for superficial sources, although the effective spatial resolution is still considered to be quite low: approximately 3-5 cm (Snyder, Raichle 2010).

Furthermore, intracranial EEG recordings demonstrate that a significant amount of brain activity does not appear in the scalp EEG (Michel, Brandeis 2010). The dipole model is an over simplification of the neural sources since extended cortical areas are often involved in the generation of scalp potentials. The relationship between the neural sources and the scalp EEG is also affected by the volume conduction effect, which further complicates the forward calculation of the scalp potentials for a given source configuration. The conductive properties of the brain, skull and scalp cause diffusion and spreading of the electrical activity from the source in all directions, but to varying degrees. The precision of the forward modeling of scalp potentials relies on the accurate estimation of the volume conduction properties of the skull, scalp and different types of tissues within the brain. Collectively, these considerations suggest that other functional neuroimaging modalities combined with EEG can play a significant role in improving our understanding of brain activity. One particularly important method is the functional magnetic resonance imaging, which has the potential to provide improved spatial localization of neural generators.
1.2 Functional Magnetic Resonance Imaging (fMRI)

Magnetic resonance imaging (MRI) is based on measuring signals caused by paramagnetic behavior of the hydrogen nuclei (i.e., protons), which are abundant in biological tissues in the form of water. The spin of hydrogen nuclei causes a small magnetic dipole. When the tissue is exposed to a strong external magnetic field such as the static magnetic field in the MRI scanner bore ($\mathbf{B}$), a small fraction of these dipoles align and form a net macroscopic magnetization ($\mathbf{M}$), which is parallel to $\mathbf{B}$. Hence, measurement of $\mathbf{M}$ can be used to build an image of the number of protons within a given volume element (voxel), otherwise known as the proton density. To measure $\mathbf{M}$, the protons inside the tissue are exposed to a radio frequency (RF) wave resulting in a process called resonant excitation. As a result of this exposure, the magnetization vector $\mathbf{M}$ is tilted from its initial direction and starts precessing around $\mathbf{B}$ in the transverse plane, orthogonal to the vectorial direction of $\mathbf{B}$. During the precession, an RF signal is induced and measured in RF receiver coils.

The tilted magnetization gradually returns to its equilibrium state in a process called “relaxation.” During relaxation, the longitudinal component of $\mathbf{M}$ approaches its initial value with the time constant $T_1$. At the same time, the transverse component of the net magnetization decays with the time constant $T_2$ due to accumulated phase differences caused by spin-spin interactions. Also, dynamic interaction between water molecules and local magnetic field inhomogeneities cause the transverse component to decay with the time constant $T_2^*$. The decay and recovery constants vary in different tissues. For instance, the $T_2^*$ decay constant for the gray matter tissue of the brain is about 60ms at 1.5T and 50ms at 3T. Hence, it is possible to achieve signal contrast between different tissue types by selection of appropriate RF sequences and timing parameters.

Rather than images acquired by proton density, or $T_1$ contrast, most fMRI techniques exploit the BOLD contrast to trace neural activities in the brain. It has been observed that based on $T_2^*$-weighted gradient echo techniques with a suitable echo time (TE), MR signal amplitudes are temporarily enhanced in regions of increased neural activity. The BOLD effect is briefly explained below.
The BOLD effect depends on the total amount of deoxygenated hemoglobin present in a brain region. Deoxy-hemoglobin is paramagnetic (i.e. it locally increases the static magnetic field). This local increase causes a distortion in the surrounding magnetic field and causes magnetic field inhomogeneities. These field inhomogeneities cause spins to precess at different frequencies, resulting in the more rapid decay of transverse magnetization (i.e. shorter T2*) and thus decreased T2* MR signal (Thulborn et al. 1982, Ogawa et al. 1990).

During a “baseline state” of brain activity (e.g. associated with the resting state, passive viewing of a simple visual stimulus, or performance of a behavioral control condition), the local concentration of deoxy-hemoglobin in the brain is relatively high due to lower local blood flow compared to an “active state” (e.g. associated with the behavioral task of interest). In the latter condition, more oxygen is transported to the site of activation via an increased cerebral blood flow (CBF), leading to a washout of deoxy-hemoglobin and thus a reduction of magnetic field inhomogeneities, which in turn leads to an increase in the local image intensity. The resulting increase in the T2*-weighted MR signal peaks after 5-7 s and returns to the initial value after 10-15 s following stimulus onset (Huettel 2009). The above variation in oxygenated and deoxygenated hemoglobin following neural activation is depicted in Figure 1.1.

![Figure 1.1: A schematic of changes in the blood flow and oxygenation level during a) rest and b) neural activity. In response to the increased oxygen demand caused by neural activity, the local vessels dilate and increase the blood flow to regions of neural activity. The increase of blood flow leads to changes of oxygenated and deoxygenated hemoglobin. The time scale of changes in relative concentration of oxygenated and deoxygenated hemoglobin following neural activity is illustrated in panel c. Source (a,b: https://www.ndcn.ox.ac.uk/, c: redrawn from (Huettel,2009)]](https://www.ndcn.ox.ac.uk/)
Changes in the levels of oxy-hemoglobin and deoxy-hemoglobin result in changes in the BOLD signal known as the hemodynamic response function (HRF). A T2*-weighted brain image thus provides a qualitative spatial representation of local brain oxygenation following increased neuronal activation. If a series of images are acquired over time then it is possible to identify temporal changes in brain oxygenation due to local neuronal firing changes. Such image sequences are created by a series of changing magnetic field gradients and oscillating electromagnetic fields, also known as a pulse sequence.

Within each image, the spatial information is coded by using gradual changes in the main magnetic field. These changes are introduced through spatial gradients, which are magnetic fields whose strength vary linearly over space. Echo planar imaging (EPI) (Mansfield 1977) is a pulse sequence that is typically used to capture temporal changes in the BOLD signal because of its speed. EPI can collect one brain volume scan following each excitation RF pulse, which enables tracking of the temporal changes of the BOLD signal in the brain.

As a result of the tradeoffs between image resolution, signal-to-noise ratio and acquisition time, at common experimental static fields of 1.5 and 3.0 T, images are acquired at a rate of 1-4 s, at 2-5 mm voxel resolution for human studies. This is generally sufficient to capture the slow hemodynamic response effect, while localizing BOLD signal in the brain.

The temporal resolution of the BOLD response is limited by the hemodynamic response, which appears as a delayed, low pass filtered version of the neuronal response. This is due to the fact that changes in the blood flow evolve at a slower timescale compared to the neural response. Thus the practical temporal resolution of fMRI remains in the order of seconds and hence cannot capture quick neuronal changes.

Functional MRI measures hemodynamic changes to localize the sources of neural response in the brain. Thus, the BOLD signal is considered only an indirect measure of neural activity, with the intermediary processes of neurovascular coupling and MRI acquisition parameters also influencing the measurement. The neurovascular coupling can causes larger vessels to have a strong BOLD signal that can be detected at a brain area distant from the original source of
activity in functional imaging. Furthermore, due to sensitivity of the BOLD signal to blood vessels, localizing the exact source of activations caused by blood vessels in a sulcus is challenging at low resolutions. Thus the specificity of the detected response also depends on the vessel size as well as fMRI acquisition method, hardware and sequence parameters (Uğurbil, Toth & Kim 2003).

To investigate the underlying neural sources of the BOLD signal, several studies have performed simultaneous intracranial recording of the electrophysiological response and the BOLD response in anaesthetized and awake monkeys (Logothetis et al. 2001, Shmuel et al. 2006, Rauch, Rainer & Logothetis 2008, Goense, Logothetis 2008). The findings of such studies have elucidated the link between the BOLD signal and the local field potentials (LFP) and multiunit action potentials (MUA). In general, the LFP and MUA measures are highly correlated due to the dense connectivity of the cortex. However, in cases where there is a discrepancy between the two measures, the LFP is shown to be a better predictor of the BOLD response. In their well-known study, Logothetis et al., dissociated the LFP and MUA responses and demonstrated that the synaptic activity reflected in the LFP is a more faithful correlate of the BOLD signal (Logothetis et al. 2001).

Although the BOLD signal activation is conventionally interpreted as a marker of neural function, in reality the fMRI signal is a complex physiological signal, and the validity of such interpretation relies on the abovementioned factors. In recent years a significant amount of research has been conducted to elucidate the relationship between invasive intracranial measurements and non-invasive measurements of human brain function such as fMRI and EEG. The goal of such research is to find non-invasive measures for interpreting neural functioning at high resolution. As both electrophysiological and imaging methods have their strengths and limitations and measure only particular aspects of brain function, an integrative approach allows us to obtain a more complete picture and improve our interpretation of both methods.
1.3 EEG-fMRI

1.3.1 Motivation:

The main objective of functional neuroimaging techniques is to detect and characterize changes in the brain states that represent neural activity. Neuroimaging techniques such as fMRI and positron emission topography (PET) detect brain activity through changes in blood flow and metabolism that follow neural activation. Although temporal resolution of these techniques is considerably lower than those that measure electrophysiological responses (such as EEG and MEG), they provide full 3D coverage of the brain at sub-centimeter resolution. Electrophysiological methods such as EEG on the other hand, are a direct measure of neural response of the brain and provide a high sampling rate in the temporal domain. However, the spatial resolution of these techniques is limited by the ill-posed nature of the EEG inverse problem and the fact that the signal can only be acquired (in a non-invasive approach) from the scalp surface. The complimentary characteristics of fMRI and EEG techniques in terms of their spatial and temporal resolution supports the combined application of EEG and fMRI to study brain response. Although the combination of the two techniques does not necessarily results in a hybrid technique with the spatial resolution of fMRI and the temporal resolution of EEG, it can significantly improve our understanding of the evolution of neuroelectrical responses in the temporal domain and related hemodynamic manifestations in the spatial domain. Integration of simultaneously recorded EEG and fMRI is likely to provide a richer spatiotemporal description of human brain function.

Combining EEG and fMRI techniques can further be justified if the brain signals recorded in both techniques originate from the same source. In (Logothetis et al. 2001) it was shown that BOLD signal modulations are more tightly coupled to LFPs than to single unit action potentials (SUA) or multi unit action potentials (MUA). LFPs are also known to be the main contributors to the scalp EEG signal. Thus, it makes sense to formulate the level of activity within brain areas as a state variable that can be imaged both as a BOLD signal and electrophysiological measure of LFP power (Logothetis et al. 2001, Logothetis 2003, Lauritzen, Gold 2003).

Simultaneous EEG-fMRI provides significant additional advantages, beyond improved space and time measures, over separate recording protocols for the same task and participant. First,
maintaining the same sensory stimulation between the two recording sessions is very challenging due to the difference in EEG and fMRI recording environments (e.g. MR scanner acoustic noise from switching magnetic gradients). Second, performance results in cognitive tasks are influenced by learning and habituation, thus rendering many tasks unsuitable for repeated testing. Third, variation in participant mood, vigilance level and behavior can be substantial between separate EEG and fMRI recording sessions. Finally, in the study of spontaneous brain activities such as those in the resting state and epileptic discharges, the fluctuations recorded with one imaging modality are unlikely to occur synchronously in time in a second session with the other modality.

A further, somewhat less obvious benefit of EEG–fMRI is that it could be used to cross-validate signal features in each recording modality. Based on knowledge derived from simultaneous EEG–fMRI it may be possible to increase our confidence in specific analysis strategies and brain response properties obtained from uni-modal recordings, which measured alone would have less convincing experimental evidence.

1.3.2 Integration strategies

The advent of simultaneous EEG-fMRI acquisition systems has also created a new area of research aiming at integrating EEG and fMRI datasets. There are a variety of approaches to combine EEG and fMRI data. While the choice of integration approach can vary depending on the area of application, background and analysis approach, the proposed methods in the literature for multimodal integration fall into three main categories: 1) Integration through prediction, where the fMRI signal is modeled using some EEG driven measures convolved with a hemodynamic response function as a predictor variable (Debener et al. 2006), 2) Integration through constraints, where spatial information from fMRI is used as a prior to initialize the source reconstruction process in EEG data (Bledowski et al. 2004, Liu, Belliveau & Dale 1998) and 3) Integration through fusion, where a common forward or generative model is used to explain both EEG and fMRI data (Calhoun et al. 2006, Daunizeau et al. 2007, Martinez-Montes et al. 2004). Below, each of these approaches is described in more detail.
1.3.2.1 Integration through Prediction (EEG-informed fMRI)

This approach is based on the assumption that the hemodynamic BOLD response is linearly coupled to the local changes in the neural activity, particularly LFPs, which are the sources of scalp EEG/ERP (Huster et al. 2012). The spatiotemporal integration between the scalp EEG signal and the BOLD signal can be achieved by investigating the covariation between EEG and fMRI activity over time. This is usually accomplished by analyzing the EEG data (in the source or channel space) and extracting one or more time courses from the data that describe the phenomenon of interest (Laufs et al. 2008). These temporal, EEG driven features are used to predict temporal fMRI responses within a general linear model (GLM). The GLM results can be used to make inferences about when and where signals from the two modalities are coupled. This approach can be adapted to study the continuously evolving phenomena in the EEG signal such as background oscillatory activity or epileptic discharges (Laufs et al. 2008), or to study variations in the EEG and fMRI signals due to human cognition (Debener et al. 2006, Debener et al. 2005, Eichele et al. 2005).

1.3.2.2 Integration via Spatial Constrains (fMRI-informed EEG)

This approach uses fMRI spatial activation patterns as a priori information to improve inverse solutions of EEG source reconstruction (Babiloni et al. 2002, Babiloni et al. 2000). The fMRI spatial patterns can also be used to select regions of activity in the cortex to create the corresponding scalp electrical distribution. The fMRI results are incorporated into the EEG source reconstruction analysis through a forward model. Such a model is established by estimating the head geometry and relevant biophysical characteristics of the brain (e.g., tissue conductivity). The complexity of these models can range from simple interleaved spheres to individually represented fine cortical patches extracted from anatomical MR images (Huster et al. 2012). The number of potential EEG source generators (i.e. the equivalent current dipoles) in these models can be inferred from the fMRI spatial activation maps. These dipoles are then seeded to locations in the brain corresponding to local fMRI maxima, subsequently allowing the time course of neural activity for each of these locations to be estimated.
1.3.2.3 Integration via Fusion (symmetrical integration)

Contrary to the two previous integration approaches, where data from one modality is used to calculate a biased estimation of the other, fusion methods use a symmetric model to assess information from both modalities at once (Huster et al. 2012). These approaches have the advantage of utilizing the full spectrum of the available information in the multimodal datasets. A number of machine learning methods have been proposed for fusion of EEG and fMRI data. A joint Independent Component Analysis (ICA) approach was applied by Calhoun et al., to examine the relationship between fMRI statistical maps and ERPs of individual participants in an auditory oddball experiment (Calhoun et al. 2006, Calhoun, Liu & Adalı 2009). Other multivariate techniques such as Partial Least Square (PLS) (Martínez-Montes et al. 2004) and Canonical Correlation Analysis (CCA) (Correa et al. 2010a, Correa et al. 2010b) have been applied to extract patterns of covariation at the signal level between the two modalities. These techniques provide an extension compared to the joint ICA approach by first extracting components from each modality and then searching for cross-modal covariation in the component space.

1.3.3 Technical considerations and challenges

Despite the history of EEG (since the 1920s) and fMRI (since the 1990s), concurrent recording of simultaneous EEG and fMRI has been feasible and practical only in the last decade, due to technical challenges associated with recording EEG data inside the MR scanner. The main drawback of simultaneous EEG-fMRI acquisition is the compromised EEG data quality. EEG data collected inside the scanner are contaminated by artifacts, which are caused by electromagnetic induction. These artifacts can be induced by rapid changes in MR gradient fields (subsequently referred to as “MR gradient artifacts”) or by pulsatile movement of blood and conductive electrodes in the static magnetic field (referred to as “Ballistocardiogram artifact”). A great deal of previous research in EEG-fMRI was devoted to developing artifact removal approaches, which have been a significant factor in the successful integration of EEG and fMRI. While the amplitude of the MR artifact can be several orders of magnitude larger than the ballistocardiogram artifact, the MR artifact is very predictable and reproducible, making it generally easier to remove from the EEG data. In this section, an overview of both types of
artifacts and the existing artifact removal approaches will be provided, followed by a discussion of safety-related issues and other technical considerations.

1.3.3.1 MR gradient artifact

The MR gradient artifact is caused by rapidly changing magnetic field gradients, which are used in EPI sequences. The gradients cause electromagnetic induction in the circuit formed by the electrodes, leads, participant and amplifiers. The amplitude of MR gradient artifacts are in the order of several millivolts, orders of magnitude larger than the normal EEG signal (10-100 µv). During fMRI acquisition, this artifact dwarfs the EEG signal and makes it unrecognizable. An example of MR gradient artifact and its effect on EEG data is illustrated in Figure 1.2. While in theory the amplitude and the shape of the artifact is invariant, under realistic conditions random variations are observable in the artifact due to small head motions of the participant. This can represent a challenge for artifact correction. However, empirical evidence from previous investigations suggests that the artifact can be reasonably assumed additive (Felblinger et al. 1999). As such, average template subtraction methods either in time (Allen, Josephs & Turner 2000) or the in frequency domain (Sijbers et al. 1999) can be effective in removing the MR artifact. In these methods, a weighted average artifact is calculated and subtracted from individual artifact instances. The template subtraction method proposed by Allen et al., has been the basis of most correction algorithms used to date (Allen, Josephs & Turner 2000). In a study by Becker et al., the performance of this method was tested by comparing the quality of visual evoked potentials (VEPs) recovered from EEG data recorded inside the scanner during scan versus scan-free periods (Becker et al. 2005). The results showed no significant difference between averaged artifact-corrected VEPs obtained from the scan period versus those from scan-free periods.

1.3.3.2 Ballistocardiogram artifact

The ballistocardiogram (BCG) artifact is the second major artifact in EEG data, becoming evident after MR gradient artifact has been removed. This artifact is generated by the cardiac pulse at frequencies of approximately 10 Hz and below (Ritter, Villringer 2006) with an amplitude that is proportional to the static magnetic field strength (Debener et al. 2008). For example, at 3T it is approximately in the range of 100-200 µv. It is commonly agreed that BCG
is predominantly caused by cardiac related body and electrode movement inside the static magnetic field (Allen et al. 1998, Goldman et al. 2000, Ellingson et al. 2004), and to a lesser extent by pulsatile changes in arterial blood flow (Müri et al. 1998). An illustration of the BCG artifact (in comparison to MR gradient artifact and the EEG signal) is provided in Figure 1.2.

Figure 1.2: Comparison of EEG data recorded inside and outside the scanner; (a) normal EEG data recorded outside the scanner in normal EEG recording environment, (b) EEG data recorded inside the scanner with the participant lying inside the scanner bore (no image acquisition). The distortion in the data is caused by the BCG artifact alone (c) EEG data recorded inside the scanner during MR image acquisition. The high amplitude of MR artifacts makes the EEG data indistinguishable.

Whereas the MR gradient artifact is highly predictable and reproducible, the BCG shows substantial variability across time, electrode channels and participants. Also, due to its biological origin the exact onset and duration of the artifact is not known a priori. Thus, removal of BCG poses a more difficult challenge compare to MR gradient artifact and is often considered the main obstacle to obtaining satisfactory EEG data quality during fMRI acquisition (Debener et al. 2008). A more detailed discussion of various existing BCG artifact removal approaches will be presented in Chapter 2.

1.4 Applications of EEG-fMRI

The last decade has witnessed a rapid growth in the application of simultaneous EEG-fMRI in different areas of neuroscience including clinical and cognitive research. The earliest application
of EEG-fMRI emerged from clinical research to localize sources of epileptogenic EEG activity in pre-surgical evaluation (Ives et al. 1993). The applications were then extended to cognitive research in resting state studies and later on to probe more complicated cognitive paradigms. The majority of research in the current EEG-fMRI literature can be divided into three categories: 1) Event-related studies, which aim to find fMRI correlates of an EEG phenomenon of interest, 2) Studies of spontaneous brain activity such as resting state and ongoing brain oscillations, and 3) Clinical applications such as epilepsy and sleep. The following sections provide an overview of the findings in each application area and discuss some of the prominent published work in each category. It should be noted that the abovementioned categories are interrelated and some of the work cited below can be discussed under multiple categories.

1.4.1 EEG-fMRI to Study the Evoked Response of the Brain

ERPs have a long history of being used in investigations of patients with neuropsychiatric disorders such as schizophrenia and depression (see (Pogarell, Mulert & Hegerl 2007) for a review). Furthermore, ERPs can be modeled in preclinical studies and can be used as translational biomarkers in the drug development process for psychiatric diseases (Javitt et al. 2008). Despite numerous applications and ongoing success of ERPs in several areas of research, all ERP analysis suffers from the limited precision in localizing neural generators involved in a particular ERP phenomenon. EEG-fMRI provides an attractive platform to study sources of specific ERP features that have been important in clinical and cognitive neuroscience research.

1.4.1.1 Visual Evoked Potentials

In the visual system, several studies have demonstrated the feasibility of recording VEPs inside the MR scanner (Becker et al. 2005, Bonmassar et al. 1999, Kruggel et al. 2000, Negishii et al. 2004, Comi et al. 2005). In general, the results of these studies suggest that average VEP can be recorded and recovered from the artifacts inside the MR scanner. However, depending on the strength of the static magnetic field, the single trial VEP analysis can be hampered by residual artifact (Debener et al. 2007).

Figure 1.3 illustrates different components of a VEP. The first component in the VEP, C1, occurs with a peak latency of 60-100ms. While the origin of C1 in the striate or primary visual cortex is generally agreed upon, the sources responsible for later VEP components such as P1
(100-130ms) and N1(140-170ms) are not well understood. Thus, one area of interest for EEG-fMRI is to provide a more precise localization for sources of the different components.

Many studies have utilized fMRI informed EEG analysis to explore sources of different VEP components. In a fMRI-constrained source localization analysis, Di Russo et al., studied sources of steady-state VEPs (generated by visual stimulus modulated at 3.5 to 75 Hz) and found two major generators in visual area V1 (primary visual area) and V5/MT (middle temporal area) (Di Russo et al. 2007). An EEG-fMRI study of VEP components by the same group using an unconstrained source modeling approach has revealed sources in the primary visual area (for C1), extrastriate area (P1/posterior N1) and parietal lobe (anterior N1) (Di Russo et al. 2002). While their results yielded good overlap between fMRI activation sites and EEG dipole locations, they also suggested that accurate source localization of components later than C1/P1 becomes more complicated and challenging.

A general assumption made in fMRI informed source reconstruction is that initial dipole placement is limited to locations with positive fMRI activation. However, this rationale was questioned in a study by Whittingstall et al., where authors compare results from unconstrained source localization to fMRI activation maps and, contrary to Di Russo et al., observed negative BOLD activation in the areas associated with P100 localization results (Whittingstall, Stroink & Schmidt 2007) (Di Russo et al. 2002).
Alternatively, some studies have used an EEG-informed fMRI analysis to localize sources of the evoked potential (EP) components. An example of this is the study by Horovitz et al., where parametric modulation of N170 component was found to be correlated with changes in fMRI activation in the fusiform gyrus (Horovitz et al. 2004). Novitskiy et al., explored the correlates of visual P1 and N1 in a spatial detection task using EEG-informed single trial analysis (Novitskiy et al. 2011). Their results showed correlates for the P1 and N1 component in the lingual gyrus, middle occipital gyrus and middle frontal gyrus. Although their results represent correlates for the contralaterality effect, they do not directly address source locations of EP components.

Localization of EP components reflecting cognitive and attention processes using EEG-fMRI have also been an active research topic. An early EEG-fMRI study of the attention effects in the visual system by Mangun et al., showed an increased BOLD signal in the posterior fusiform and middle occipital gyri associated with an increase in spatial attention (Mangun et al. 1998). This was accompanied with an attention related modulation of the P1 component. While Mangun et al., found no attentional modulation of the BOLD signal in the primary visual (V1) area, another study by Martinez et al., found divergence between fMRI and EP results, with fMRI activations showing attention related modulation in primary visual cortex (Martinez et al. 1999). A follow up study by Di Russo et al., revealed that earlier VEP components such as C1, which are typically localized to V1, are not affected by attention modulation. However, they discovered a later component (150-225ms) that was localized to V1 and demonstrated a reversal in polarity between upper and lower visual field stimulation, suggesting a spatial attention related effect (Di Russo, Martinez & Hillyard 2003).

Another well-studied component is P3 (300-600ms), which is associated with target detection in oddball paradigms. Studies on localizing this components using EEG dipole modeling have yielded inconsistent results (Bledowski et al. 2004). While increasing the number of dipoles in the model can provide satisfactory results in terms of explaining the variance in the EP, it can also result in solutions with quite different dipole positions (Mulert 2010). Consequently, several studies have used EEG-fMRI to apply fMRI-constrained EEG source localization of the P3 component (Bledowski et al. 2004, Crottaz-Herbette, Menon 2006). These studies investigated the sub-components of P3 (i.e P3a and P3b) separately. Their results suggest a broadly distributed network of sources for these components with insula and precentral sulcus
and anterior cingulate cortex showing a stronger association with P3a and inferior parietal areas showing a stronger association with P3b.

Overall, while source localizing EEG-fMRI studies of cognitive ERP components have yielded more coherent results, findings of the sensory experiments show less consistency. This is in part due to differences in the experiment designs used in each study, which makes direct comparison of the results challenging.

1.4.1.2 Auditory Evoked Response

Simultaneous EEG-fMRI recording of auditory response poses additional challenges due to scanner acoustic noise. A potential solution to this problem is to adapt a sparse sampling fMRI acquisition protocol, where the auditory stimuli are presented during silent periods of scanning protocol (Hall et al. 2000). However several studies have successfully performed continuous simultaneous recording protocols to probe sources of auditory evoked potentials (AEPs). The first such study was conducted by Liebenthal et al., to investigate the mismatch negativity (MMN) in a passive auditory oddball paradigm (Liebenthal et al. 2003). MMN is a negative ERP component with a typical latency of 150-250 ms and is generated in response to an odd stimulus in a sequence of sensory stimuli (Garrido et al. 2009, Näätänen, Gaillard & Mäntysalo 1978).

Liebenthal et al., demonstrated consistency between MMN components recorded inside versus outside of the MR scanner in terms of reactivity to parametric modulation and topographical distribution. Furthermore, changes in the MMN magnitude was found to be correlated with increased BOLD signal in right superior temporal gyrus and right superior temporal plane. In a more recent study of the auditory MMN, Sabri et al., used EEG-fMRI to investigate the influence of task difficulty on MMN amplitude and fMRI response. Their results revealed that the superior temporal gyrus and sulcus were more strongly activated in the more difficult auditory task (Sabri et al. 2006).
An illustration of waveform and components of the auditory evoked potentials is provided in Figure 1.4 above. In a simultaneous EEG-fMRI study of the auditory oddball paradigm, Mulert et al., compared the amplitude of auditory EP components for inside versus outside scanner recordings (Mulert et al. 2004). While the earlier N1/P2 component was reduced inside the scanner, the P3 amplitude remained unaffected. A comparison of independently analyzed EEG and fMRI data revealed concordance between source localization foci and fMRI activations for P3 components in temporoparietal junction, frontal areas, and the insula. These findings were further extended by (Debener et al. 2007) and (Otzenberger, Gounot & Foucher 2005) who showed that separate auditory P3 components (P3a and P3b) can be discriminated using simultaneous EEG-fMRI recordings. In a single trial analysis of the auditory oddball paradigm Benar et al., demonstrated a positive correlation between the amplitude of P3 and the fMRI signal in the anterior cingulate cortex and a negative correlation between P3 latency and fMRI activation in medial frontal regions (Bénar et al. 2007).

Although most auditory studies in the EEG-fMRI literature have focused on the later cognitive components of auditory EPs (e.g. P3, MMN), there is evidence of a relationship between earlier
sensory evoked responses, such as N1, and the BOLD response. For instance, Mulert et al., showed the amplitude of auditory N1 component and the BOLD signal in the primary auditory cortex were modulated by the sound intensity level (Mulert et al. 2005). Furthermore, the authors reported that variations of the N1 amplitude were found to be correlated to that of BOLD signal in the primary auditory cortex. A single trial analysis of the EEG and fMRI auditory responses by Mayhew et al., revealed neither significant correlation between N1 nor P2 amplitude and BOLD fMRI in the primary auditory area. However the authors did report a correlation across participants at the group level between N1 amplitudes and the BOLD response in bilateral auditory cortices (Mayhew et al. 2010). In another study, Scarff et al., used an interleaved acquisition protocol and high-density EEG array to compare the anatomical sources of the N1 generators. While the mean dipole locations from the source reconstruction analysis overlapped with the centre of gravity of the BOLD response in the horizontal plane, the authors reported mismatches in the axial location of the mean equivalent dipole and fMRI activity as well as unmatched asymmetrical fMRI activation patterns (Scarff et al. 2004).

In summary, while the cognitive auditory paradigms such as auditory oddball and MMN has been extensively studied in the EEG-fMRI literature, fewer studies have examined the sensory auditory evoked potential components. The disturbance from the MR scanner noise makes the study of these components even more challenging. Hence the neural sources for these components and their relationship to the BOLD response required further investigation.

1.4.2 Oscillatory/Spontaneous activity

Studies of brain oscillatory activity (i.e., brain rhythms) aim to analyze ongoing spontaneous brain signals rather than averaged or induced brain activity. The majority of research in this area focuses on resting state brain activity. Though it may seem counter intuitive, knowledge of the spontaneous resting state brain activity can improve our understanding of task related responses. In fact, it has been suggested that intrinsic cortical fluctuations account for variability in task responses through addition to purely task-induced activity (Fox, Raichle 2007). There is also evidence of networks that are active during the resting state (e.g., the default mode network) whose level of coherent activity (or lack thereof) during rest can be indicative of normal or
pathophysiological brain states. Studying the origins of brain oscillations thus provides insights to healthy and pathological brain function (Laufs 2009).

One of the challenges associated with unimodal studies of spontaneous activity (e.g., in the resting state) is that interpretation of the recorded signal in the absence of a distinct phase locked behavioural task response remains subjective and inaccurate. Simultaneous EEG-fMRI recording of spontaneous brain activity provides a second measure that can be used as an additional perspective to interpret brain activity.

Alpha rhythms are the most prominent and well studied rhythms of the brain that occur in the 8-12 Hz frequency range during a wakeful rest state. Unsurprisingly, the first EEG-fMRI studies of brain oscillations concerned the study of BOLD correlates of alpha rhythm in the resting state. The analysis approach in most EEG-fMRI studies of the brain rhythm is based on the assumption that neural activity is reflected in the BOLD signal via convolution with some known or measureable hemodynamic response function (Ullsperger 2010a). In such approaches, the EEG measure, which is often the amplitude of the oscillatory band of interest, is used as a regressor in a general linear model to predict fMRI activation patterns. In the following paragraphs some of the literature on EEG-fMRI studies of alpha rhythm during the resting state will be discussed.

The first investigations of alpha-BOLD relationships during resting state (Goldman et al. 2002) reported a positive correlation between the amplitude of the alpha power and the BOLD signal in the thalamus and negative correlations in the occipital-parietal regions. These findings conformed to results from animal studies and were replicated by other groups (Feige et al. 2005, de Munck et al. 2007, Mantini et al. 2007, Moosmann et al. 2003). However, inconsistent results and inter-individual differences have emerged as recurrent themes in this literature. For instance, some studies have also reported negative correlation patterns in frontoparietal regions (Laufs et al. 2003b, Laufs et al. 2003a, Laufs et al. 2006, Goncalves et al. 2006), pointing to a more global and modality-independent role of alpha rhythm in vigilance.

Besides the alpha rhythm, a number of authors have investigated the functional role and cellular substrate of the theta rhythm during resting state. Previous EEG findings have repeatedly demonstrated increased midline frontal theta activity during cognitive performance to be associated with mental effort (Başar et al. 2001). A recent study by Scheeringa et al., conducted
simultaneous EEG-fMRI of the resting state and found the midline frontal theta rhythm to be negatively correlated with the BOLD signal in the default mode network (Scheeringa et al. 2008). Similar results were reported by Mizuhara et al., who investigated BOLD correlates of midline frontal theta during rest as well as a task condition (mental calculation), and found negative correlations in regions corresponding to the default mode network (Mizuhara et al. 2004).

In recent years, a few studies have expended upon these single-band analysis approaches to probe EEG-fMRI relationships (Mantini et al. 2007, Laufs et al. 2006). Instead of extracting only the alpha or theta rhythm, the authors have included other frequency bands simultaneously to examine the EEG-BOLD association. By using this approach Laufs et al., were able to explain differences in the EEG-BOLD correlation patterns in their earlier report (Laufs et al. 2006)(Laufs et al. 2003a). The new analysis results revealed that participants with more prominent occipital correlation showed greater relative theta power and participants who demonstrated a frontoparietal correlation had higher relative beta power (Laufs et al. 2006). In the same vein, Mantini et al., performed a data-driven analysis of the resting state to find electrophysiological signatures of ICA components of the fMRI resting state network. Each functional network was characterized by a combination of EEG power variations in the delta, theta, alpha, beta and gamma band (Mantini et al. 2007). Several findings from this study were consistent with previous results including those initially reported by Laufs et al., which suggested a negative alpha-BOLD correlation in the occipital area and positive beta-BOLD correlation within parts of the default mode network (Laufs et al. 2003a).

The functional role of the posterior alpha rhythm for visual processing has been a subject of debate. To study the influence of ongoing occipital alpha power on the fluctuations of the evoked visual BOLD signal in the visual cortex, Becker et al., (Becker et al. 2011) conducted an EEG-fMRI study and compared the magnitude of the hemodynamic BOLD response to visual stimulation between high and low alpha states. Their results suggested a negative relationship between pre-stimulus alpha power and amplitude of the evoked BOLD response in parts of the extra striate cortex. Furthermore, this relationship was characterized as a linear superposition in sub regions of the visual cortex. In a similar study, Scheeringa et al., found no correlation between the amplitude of the occipital alpha power and the visual BOLD response, but observed
a relationship between the phase of alpha power at the stimulus onset and the BOLD (Scheeringa et al. 2011). In a follow up study, Mayhew et al., investigated the link between occipital alpha power and the BOLD signal during rest and visual stimulation (Mayhew et al. 2013). The fMRI patterns associated with resting state included mostly areas in the default mode network and agreed with previous findings of resting state studies. In the visual cortex, their results replicated those from Becker et al., in terms of existence of an inverse relationship. However, contrary to the results from Becker et al., the location of the relationship was reported in the primary visual cortex (Becker et al. 2011). Thus, the impact of posterior alpha rhythm and its associated BOLD signal on modulating of task-induced response in the visual system remains unclear.

In the cognitive domain, simultaneous EEG-fMRI studies of ongoing brain oscillations have revealed important information about the underlying brain dynamics of cognitive functions such as memory and attention. Schireeinga et al., examined the BOLD correlates of alpha and theta power estimates during a working memory task and observed an increase in the right posterior alpha power, which was functionally related to BOLD signal decrease in the primary visual cortex and posterior middle temporal gyrus (Scheeringa et al. 2009). They also observed an increase in frontal theta power that was correlated to decreased BOLD in regions of the default mode network. These findings were extended by Michels et al., who added higher frequency bands (i.e. beta and gamma) to their analysis and found mostly positive correlation patterns (with the exception of beta1) in dorsolateral prefrontal cortex, medial prefrontal cortex (gamma), and inferior frontal gyrus (beta2/gamma) (Michels et al. 2010). The correlation patterns for the lower frequency bands matched the results reported from previous studies (Scheeringa et al. 2009). In studies of attention, EEG-fMRI has been used to distinguish sources of gamma activity associated with decision making versus visual processing (Castelhano et al. 2014) and to study the functional role and BOLD correlates of alpha rhythm that modulate the task response in auditory stimulation (Walz et al. 2015).

1.4.3 Epilepsy

Epilepsy is a neurological disorder that affects the nervous system and causes seizures. It affects 5 to 10 in every thousand persons and 30% to 40% of patients experience seizures despite
medical treatment (Kwan, Sander 2004). Seizures are episodes of disturbance in the electrical activity of the brain, which involve sudden, excessive and rapid discharges of grey matter. Depending on the origin and the extent of the abnormal electrical activity, seizures are divided into two main categories: 1) Focal seizure, where the epileptic electrical discharges initiate in one part of the brain and then spread to other region. 2) Generalized seizures, where the epileptic discharges do not have an identifiable source, appear bilaterally and symmetrically and affect all or most of the brain. Due to the vast extent of the literature and differences in underlying mechanisms and manifestations of adult versus childhood epilepsy, the following overview focuses on the impact of EEG-fMRI in adult epilepsy.

Over the last decade EEG-fMRI has been applied to study neural and physiological sources of ictal and interictal epileptic activity (see (Chaudhary, Duncan & Lemieux 2013) for a recent review). Although the onset of the epileptiform activity can be clearly detected in the EEG signal, the location of neural sources from which this pathologic activity spreads in the cortex cannot be inferred from the EEG signal due to its limited spatial resolution. Similarly, the application of fMRI alone to study hemodynamic correlates of seizure poses major challenges. The ictal changes in the BOLD signal are slow, widespread and difficult to interpret. Hence detecting the onset of abnormal activity relies on the visual monitoring of the patient (Jackson et al. 1994, Detre et al. 1996, Detre et al. 1995, Krings et al. 2000). The concurrent recording of EEG and fMRI for presurgical evaluation of epilepsy provides insights beyond what is possible with separate recording protocols (Mulert, Pogarell & Hegerl 2008, Gotman et al. 2006, Gotman, Pittau 2011). The application of simultaneous EEG-fMRI in adults with epilepsy has two main objectives: 1) to localize the sources of epileptiform activity and improve the efficiency of the surgical treatment (Federico et al. 2005a, Federico et al. 2005b, Salek-Haddadi et al. 2006, Thornton et al. 2010, Zijlmans et al. 2007), and 2) to improve our understanding of the relationship between generators of the electric epileptic activity and the hemodynamic response in focal (Bagshaw et al. 2004, Jacobs et al. 2009, Kobayashi et al. 2006) and generalized epilepsy (Hamandi et al. 2006, Gotman et al. 2005, Aghakhani et al. 2004).

Due to safety considerations and practical challenges associated with simultaneous recording of ictal activity (i.e. during the seizure), the EEG-fMRI literature of epilepsy is dominated by studies of interictal activity of the brain. In these studies, the most common approach to combine
EEG and fMRI data is to extract the hemodynamic activation. The onsets of the spikes are usually incorporated as regressors in a GLM model to reveal patterns of hemodynamic response. Accordingly a number of studies have applied this technique and similar approaches to localize sources of epileptiform activity in the brain (Salek-Haddadi et al. 2006, Lemieux, Krakow & Fish 2001, Salek-Haddadi et al. 2003, Gotman, Bénar & Dubeau 2004).

While previous studies have demonstrated a spatial overlap between intracranial recording of electric epileptiform activity and the corresponding hemodynamic response in focal epilepsy (Salek-Haddadi et al. 2003, Bénar et al. 2002), the quantitative relationship between epileptic EEG activity and the hemodynamic response seem to vary in shape and amplitude across patients, brain regions and type of the epileptic activity (Bénar et al. 2002). In a number of continuous EEG-fMRI studies by Salek-Haddadi et al., focal unilateral subclinical seizures were found to be associated with grey matter activations (Salek-Haddadi et al. 2002) while generalized epileptic discharges showed positive correlation with BOLD signal in the thalamus and symmetrical negative correlation in the frontal regions (Salek-Haddadi et al. 2003).

In conclusion, EEG-fMRI can provide important information about the location of sources and spread of the epileptic activity. It has improved our understanding of neurovascular coupling mechanisms in epilepsy. However, the variability of the fMRI hemodynamic response to different types of epileptic neural activity should be considered in the data analysis.

1.5 Summary

Simultaneous EEG-fMRI is the integration of two of the most prevalent non-invasive functional neuroimaging techniques, EEG and fMRI. It combines the complementary temporal and spatial features of the two modalities and enables concurrent study of neural and physiological responses of the brain. During the relatively short history of the technique, the number of publications in the field has grown exponentially in different areas of neuroscience research. Over the last decade EEG-fMRI has become a promising technique to address a wide range of research questions in clinical and cognitive neuroscience. Despite all the progress in the field up to date, many technical and scientific questions remain open.
A major challenge in concurrent EEG-fMRI acquisition is the artifacts in the EEG data from the MR scanner environment. While the artifact removal techniques have come a long way, the choice of the best artifact correction method and the optimum parameters require further investigation. This is particularly important for the BCG artifact, which is more unpredictable due to its biological origin than the MR gradient artifact. A large body of EEG-fMRI literature is devoted to evaluating and comparing the performance of proposed artifact removal methods (Debener et al. 2007, Vanderperren et al. 2010). A study by Debener et al., showed how three different methods of BCG artifact removal can result in different auditory N1 amplitudes and SNRs (Debener et al. 2007). A more recent study by Vanderparren et al., offers perhaps the most comprehensive systematic evaluation of different BCG artifact removal methods (Vanderperren et al. 2010). In this study authors compared the performance of three main artifact removal techniques (average template subtraction, principal component analysis (PCA) and ICA) across a range of metrics. However, what they and the current literature on BCG artifact removal techniques failed to take into account is the variability of the artifact across participants and channels. The amplitude and shape of the artifact in every channel varies depending on the channel’s location, the level of participant motion and the position of the participant’s head inside the scanner (Mullinger, Yan & Bowtell 2011). Furthermore, the optimal choice of correction parameters and technique also depends on the experiment design and strength of the response. While weaker and less obvious responses can potentially benefit from a more aggressive correction approach, phenomena with more prominent responses are prone to over correction. The second chapter of this thesis will provide a more detailed overview of the current state of the literature in BCG artifact removal and proposes a new approach that takes into account sources of variability in the BCG artifact, thus significantly improving the SNR.

Turning to the applications of EEG-fMRI, localizing sources of ERP components has been an attractive research topic since emergence of the technique. As discussed above, researchers have adopted EEG-informed fMRI or fMRI-informed EEG analysis approaches to identify sources of cognitive and sensory ERP components. While BOLD correlates of later cognitive components are generally agreed upon in the EEG-fMRI literature, there is a lack of consensus when it comes to sources of sensory evoked responses. One of the reasons behind these discrepancies may be the shortcomings inherent to the integration approaches used to date. While there is substantial evidence of the coupling between electrophysiological and BOLD responses (Logothetis,
Pfeuffer 2004), there are several situations in which a one-to-one relationship between the scalp EEG and the BOLD signal cannot be expected. For example, neural activity can result in detectable changes in the BOLD signal but not the scalp EEG signal if the spatial orientation of the electrical generators forms a closed-field geometry leading to cancellation of current flow (Nunez, Silberstein 2000). On the other hand, highly synchronous neuronal activity in a small region of the brain may lead to detectable EEG signal at little or no metabolic cost. Hence the associated hemodynamic response may be too small to be detected or survive statistical significance thresholds (Huster et al. 2012). In these scenarios, using data from one modality to predict or constrain the analysis of the other modality can limit the validity or even incorrectly bias the results. A second possible factor that can contribute to difficulties in the source localization results is that the underlying mechanisms that influence the fluctuations in the response amplitude or the coupling between EEG and BOLD signal may be different at the individual participant and group levels. Whereas in most of the existing literature, the within and between participant effects are confounded and intertwined.

In Chapter 3 of this thesis, a symmetrical analysis approach is used to identify sources of different components of visual and auditory evoked potentials. In this analysis approach, EEG and fMRI data are analyzed independently and their relationship is evaluated using a univariate regression technique. Also, the data is analyzed at two distinct levels to study the EEG-BOLD relationship at between and within participant levels.

While the traditional ERP-BOLD analysis involves searching for BOLD correlates of the phase-locked EEG response (which are represented by ERPs), it has been argued that spectral analysis of the brain response can be a more suitable approach for relating stimulus- and task-related neuronal activity to perception and cognition (Siegel, Donner 2010). Brain processes are not limited to phase-locked (i.e. same latency and polarity) responses, they also include non phase-locked activity manifested across different frequency bands. Alternatively, the time-locked response is a more general measure of brain’s activity and encompasses both phased-locked and non-phase-locked responses. The time-locked response is measured in the spectral domain and, compared to the phase-locked response, may provide a more comprehensive picture of correlation between the neuroelectric activity and the BOLD signal. This idea is supported in
theory (Kilner et al. 2005, Donner, Siegel 2011) as well as by invasive (Logothetis et al. 2001, Siegel et al. 2007) and non-invasive (Hall et al. 2005, Brookes et al. 2005) studies.

In Chapter 4 the relationship between time-locked EEG spectral responses and the BOLD response to auditory and visual stimuli is examined in an extension of the results of Chapter 3. Furthermore, a multivariate framework based on partial least squares (PLS) is introduced for symmetric analysis of EEG and fMRI data. In conventional asymmetric approaches, temporal information derived from the EEG data is correlated with fMRI data using a GLM approach. However, the integration method proposed in Chapter 4 analyzes both datasets concurrently rather than sequentially. The proposed method has the added advantage of the multivariate PLS analysis, which enables searching for correlation patterns in high dimensional data.

Another important question that has been the focus of multiple research studies involves examining interactions between ongoing and event-related, evoked responses in the brain. As discussed above, a large body of literature has investigated the relationship between ongoing oscillatory EEG activity and the BOLD signal. However, very few have examined the relationship between oscillatory EEG activity and the BOLD evoked task response. While the majority of previous studies have emphasized a limited window of the spectral signature at a limited electrode site, namely the occipital alpha rhythm, a few recent studies have demonstrated that including other frequency bands in the analysis explains some of the inconsistencies in the previous findings (Mantini et al. 2007, Laufs et al. 2006). A potential explanation could be that ongoing dynamic brain activity results in a range of spectral signatures, which are manifested across different frequency bands and electrode sites. Furthermore, an increase or decreases in the occipital alpha power might be common to different brain states, and consequently different fMRI activation patterns.

The analysis in Chapter 5 addresses these issues by incorporating unlocked spectral and spatial EEG information in an extension of the analysis in Chapter 4. The efficiency of PLS in handling high dimensional datasets makes it feasible to include EEG features across multiple frequency band and electrode locations simultaneously in the model and to perform a concurrent analysis with the fMRI data.
In both Chapters 4 and 5 the classical PLS analysis is extended to improve the generalizability of the results by running the PLS analysis within a predictive, cross-validation framework to obtain more than simple association measures (Gabrieli, Ghosh & Whitfield-Gabrieli 2015, Dubois, Adolphs 2016).

In Chapter 6 I will discuss further possible methodological improvements in artifact removal by developing new adaptive correction algorithms. I will also point out potential applications of the cross-validated PLS-based framework to study the relationship between ongoing EEG and BOLD response in the context of cognitive paradigms (Babiloni et al. 2000).

With the exception of specific contributions from my colleagues mentioned in the acknowledgement section, all the steps involved in producing the results presented throughout this thesis (i.e. experiment design, data collection, methodological developments and data analysis) was performed by me.
Chapter 2 : EEG Analysis Methods and Artifact Removal for Simultaneous EEG-fMRI


2.1 Introduction

As it was pointed out in the previous chapter, the major drawback of simultaneous EEG and fMRI recording is the compromised EEG data quality. The EEG signal recorded inside the MR scanner is contaminated by two main sources of artifacts, which are created as a result of time dependent magnetic field changes inside the MR scanner: The MR gradient artifact and the Ballistocardiogram (BCG) artifact.

The gradient artifacts are created by the rapid switching of the MR gradients during data acquisition. These artifacts have amplitudes of the order of milivolts and completely obscure the EEG signal. Despite its large magnitude, the MR gradient artifact in stable scanners is relatively time invariant and can be corrected by subtracting an average artifact template from the ongoing EEG (Allen, Josephs & Turner 2000, Garreffa et al. 2004). Previous studies have demonstrated that optimal template subtraction efficiently removes the MR gradient artifact and enables recovery of the evoked potentials (Becker et al. 2005) as well as ultrafast evoked oscillations (Freyer et al. 2009).

Contrary to the MR gradient artifact, the BCG artifact is time-variant, i.e., the shape and scale of this artifact as well as its spatial distribution is variable over time. Also, in many cases the main frequency content of the artifact (0.5-25Hz) overlaps the spectrum of the EEG signal of interest (Debener et al. 2007). The abovementioned factors turn removal of the BCG artifact into a more difficult challenge. Although the exact underlying mechanism of generation of the BCG artifact
is still in dispute (Yan et al. 2010), it is predominantly attributed to the pulsatile movement of the electrodes due to cardiac activity inside the static magnetic field of the MR scanner.

Artifact correction methods for BCG are primarily based on two algorithms. The first group of algorithms are based on the method of average artifact subtraction (AAS) (Allen et al. 1998). In this method instances of BCG artifacts are identified by detecting peaks in the ECG signal that pass a certain amplitude threshold. Once individual artifact instances are marked, a channel-wise artifact subtraction is run on the EEG data. To correct for each artifact instance, an average artifact template is calculated over a time window preceding the target artifact and subtracted from it. Other variations of this technique include applying median filtering or a Gaussian weight function across the BCG time window before averaging (Goldman et al. 2000, Ellingson et al. 2004). A problem with this technique is that variation of the BCG artifact throughout the recording session can leave residuals in the EEG signal. The second BCG artifact removal approach was proposed by Niazy et al. (Niazy et al. 2005) and does not make any assumptions about the stability or stationarity of the BCG artifact across time. This method, called optimal basis selection (OBS), uses Principal component analysis (PCA) to model and remove the artifacts from the EEG data. An artifact template is created using a selected number of principal components (PCs) and subtracted from each artifact instance. One common characteristic of both algorithms is that they do not use topographical information of the artifact for correction. Alternative approaches have been proposed using source separation techniques, most notably independent component analysis (ICA), using the spatial distribution of the artifact and its evolution to distinguish and remove the artifact from the data (Eichele et al. 2005, Bénar et al. 2003). However, the non-stationary topography of the BCG artifact reduces the effectiveness of such spatial ICA-based approaches (Debener et al. 2007, Vanderperren et al. 2010).

With the emergence of various artifact removal algorithms, the need for systematic evaluation and comparison of the existing methods has become critical. There is however little consensus in the literature on the optimal choice of technique and parameters.

The correction of BCG artifacts with ICA is based on creating spatial filters that separate sources of artifact from the EEG data. However, the dynamically changing distribution of the BCG artifact makes ICA unsuitable for extracting the sources of artifact. In a study by Debener
et al. a comparison of BCG correction was performed with OBS, ICA and their combination. In this study each algorithm was implemented with default parameter settings to remove BCG artifacts from a dataset containing auditory evoked potentials. The results of the study showed that applying ICA without any prior processing resulted in a reduced amplitude and signal-to-noise ratio (SNR) of the evoked potentials compared to the uncorrected data and unsatisfactory dipole modeling results.

Vanderparren et al. performed a comprehensive study of optimizing parameter settings for BCG artifact removal with ICA. They investigated the choice of parameters and different implementations of OBS, ICA and their combination (OBS-ICA) and evaluated the quality of resulting visual evoked potentials. They concluded that even after fine tuning the ICA parameters, which is a non-trivial and crucial step, the performance of ICA was not significantly better than OBS (Vanderperren et al. 2010). The combination of OBS and ICA resulted in some improvements over application of ICA alone. However, the improvement was found to be inconsistent and sometimes produced poorer SNRs. Based on these results evaluation of the performance of ICA is not included in the current study.

In their study, Vanderparren et al. also tested the effect of using different numbers of PCs at the artifact modeling stage of the OBS algorithm. They examined a range of PCs from the algorithm’s default value (3 PCs) to 7 PCs (Vanderperren et al. 2010). However, this type of optimization at the group level fails to capture the differences in the individual participants’ data. In fact, since the amplitude, shape and variability of both evoked potentials and the artifact are different from participant to participant, and to some extent trial-to-trial, the optimum choice of technique and parameters could be different for each dataset.

This chapter aims to identify the optimal selection of the available techniques and parameter values for effective artifact removal from EEG data recorded in the MR scanner. First, I will provide a comparison of the available MR gradient and BCG artifact removal pipelines as implemented in two of the most commonly used packages: Brain Vision Analyzer-II and EEGLab. I tested the performance of these pipelines on the SNR of the auditory and visual evoked potentials (EPs) recorded during fMRI acquisition. Furthermore, I tested whether combining artifact removal stages from different packages has any effect on the quality of the
cleaned data. Second, I optimized the parameters in the correction algorithms for each individual EEG dataset. In particular I examined the effect of a wide range of PCs 3-25 in the OBS algorithm. The results suggest that taking into account between-participant and between-run variability can result in significant gains in the SNR of the EPs, and the data quality in some cases is comparable to that of data recorded outside the scanner.

Once MR gradient and BCG artifacts are removed from the EEG data, multiple analysis steps are applied to the EEG data to extract the averaged evoked response of the brain. An overview of these steps is provided in Figure 2.1 and they will be described in more details throughout the chapter. Furthermore, this chapter covers the experimental paradigm designed to collect the dataset that was used in this thesis.

2.2 Materials and Methods

2.2.1 Participants

The data used in this thesis was collected during three phases. During phases one to three 10, 6 and 4 participants were recruited respectively. The results provided in this chapter are based on analysis from participants from phase one and two of the recruitment (N = 16). Participants were young healthy adults (8 male, age range 21-31 years; Mean =25, Standard Deviation (SD) = 3.2) without any history of neurological disorders based on self report. All participants provided informed written consent in accordance with guidelines set by Baycrest’s Research Ethics Board.

2.2.2 Stimuli and procedure

This chapter covers the basic information about the experimental paradigm and stimuli specifications. A more detailed description of the technical aspects of the experiment such as the stimulus timing sequence will be provided in the next chapter.

A continuous, rapid event-related paradigm was used for stimulus presentation. Alternating, left and right unilateral visual and auditory stimuli with durations of 200 ms were presented in a random order with inter stimulus interval (ISI) randomly varying from 1 to 7 seconds. The visual stimulus was a checkerboard that flashed on the left or right side of the screen, vertically centred with a contrast of 100%. The auditory stimulus was a harmonic complex tone (200 ms in duration, 10 ms rise/fall time) with a fundamental frequency of 200 Hz presented at the right or
left ear at about 85 decibel (dB) sound pressure level (SPL). The participants were instructed to pay attention to the stimuli, but no response was required during the task. During each run, 65 interleaved trials were presented of each condition (left visual, right visual, left auditory and right auditory). Each recording session consisted of three runs of approximately 10 minutes each inside the scanner followed by an additional run recorded outside of the scanner. At the beginning of each run 30 seconds of data was recorded before starting the fMRI data acquisition. This data was later used in the BCG artifact removal step.

2.2.3 Data acquisition

FMRI data were collected using a T2* weighted pulse sequence on a 3T Siemens scanner with a 12 channel head coil. In each run, 320 time points were collected with TR = 2s, TE = 30 ms, flip angle 70°, field of view (FOV) 20×20 cm, 64x64 matrix, number of slices = 28, slice thickness = 5mm.

EEG data were recorded using the BrainVision, fMRI compatible, 64-channel EEG cap and amplifiers, and BrainVision Recorder software (BrainProducts, Munich, Germany). EEG was recorded from the scalp at a 5 kHz digitization rate and was fed to the amplifiers inside the scanner room. One channel of the electrode cap was used to record electrocardiogram (ECG) data with the corresponding electrode attached to the participant’s back close to the heart. All of the recording channels were referenced to the midline central electrode (Cz). EEG signals from the frontal electrodes (FP1, FP2, FPz) were used to detect and remove eye movements. The impedances between electrodes and scalp were kept below 10 kΩ. The fMRI compatible amplifiers were placed inside the scanner bore and the wires that connected the cap with the amplifier were adjusted to an optimal location and fixed in their position with sand bags to minimize vibrations. The digital output from the amplifiers was fed via optical cables into a computer outside the scanner room. During the recording a Syncbox was used to synchronize the sampling clock of the EEG recordings to the scanner’s internal clock. The MR scanner fan was turned off during the acquisition to reduce the potential contamination of the EEG signal. However the cooling hydrogen pumps remained on throughout the scan. The latter ventilation system is suggested to cause artifacts >40Hz in the EEG data. Since high frequency signal information was not a focus in this work, the pumps remained on and the EEG signal was filtered at 30Hz in the processing (see 2.2.4 for more details).
Figure 2.1: Block diagram of basic EEG processing steps.
2.2.4 MR gradient artifact removal

I separately tested two conventionally used methods of MR gradient artifact removal. These were average template subtraction (AAS) (Allen, Josephs & Turner 2000) and fMRI slice template artifact removal (FASTR) (Niazy et al. 2005), as implemented in BrainVision Analyzer-II (Brain products, Germany), and the EEGLab (Delorme, Makeig 2004) plugin from FMRIB (Oxford, UK), respectively. In the following section these methods are explained in more detail. The correction procedures described below were applied to individual runs for each participant.

2.2.4.1 AnalyzerII

The gradient artifact removal method implemented in Analyzer-II is derived from the average artifact subtraction method (Allen, Josephs & Turner 2000).

The onset of each volume artifact was marked in the EEG data by a special trigger received from the scanner at the beginning of volume acquisition. These markers were used to divide the EEG data into 2000 ms segments that were time locked to the markers and contained one volume artifact. For each channel, an initial average volume artifact template was calculated from 5 volume artifacts (i.e., 5 TRs) at the beginning of each run (after discarding the first 10 initial volumes). Subsequent volume artifacts were used to update the artifact template if the correlation between the artifact and the template exceeded 0.975. Then, a channel-wise artifact correction was performed by subtracting the artifact template from individual instances of the volume artifact. After removing the artifact, the EEG data was band-pass filtered at 0.5-40Hz and down sampled to 250Hz.

2.2.4.2 EEGLab

The EEG data was also processed in parallel for gradient artifact removal with FASTR: a slice-based artifact removal approach (Niazy et al. 2005). The onset of each slice artifact was marked by a slice event marker in the EEG data. Then the data was up-sampled to 20 KHz and all slice artifacts were aligned to the first artifact to correct for possible jitter in the onset of the artifacts. An average artifact template was calculated in a sliding window of 30 slice artifacts and subtracted from the centre slice artifact. Residuals remaining after template subtraction were
segmented, time-locked to the slice event and stacked in a matrix for running PCA. The first four PCs resulting from this analysis were used as a set of “basis functions” to represent the variations of artifact residuals. These basis functions were then used to model and subtract the residuals from individual artifact segments.

The final stage of FASTR is an optional adaptive noise cancellation (ANC) filter. Including this step in the artifact removal process can enable further removal of the artifact residuals. However, our preliminary results suggested that in some cases enabling the ANC can cause disruption in the spectrum of the cleaned EEG data and weaken the underlying evoked response. This effect was more prominent in participants whose evoked response spectral power was close to slice acquisition frequency (15Hz). Consequently, to test the effect of ANC on the quality of evoked potentials, the correction was run with and without including ANC in the pipeline.

2.2.5 BCG artifact removal

For BCG artifact removal, techniques implemented in Analyzer-II and EEGlab were tested on the data separately. To evaluate and compare the performance of peak detection methods in the two packages one run from each participant was used for manual peak inspection. During the inspection process the presence and location of a cardiac pulses detected by the two methods were compared against results of manual pulse detection. The number of false positives and false negatives detected by both methods were counted while using the manually detected location of the peak as the ground truth.

The following sections describe these techniques and the optimization approach in more detail. Similar to the MR artifact correction step, all procedures described below were performed on individual runs for each participant.

2.2.5.1 Analyzer-II

The artifact removal technique implemented in Analyzer-II is based on the average artifact subtraction method (Allen et al. 1998). BCG artifacts were detected using data from the ECG electrode channel. Within the 30s pre-scanning period, one of the BCG artifacts was selected as the initial artifact template. This template was then used to search for subsequent occurrences of the BCG artifact in the ECG channel after the pre-scanning period.
New BCG artifacts were identified using two criteria: First, a minimum correlation value of 0.6 between the template and the potential artifact. Second, an amplitude ratio of 0.35 to 1.5, which ensures at every point the amplitude ratio of the template to the ECG signal remains between 0.35 to 1.5. A BCG artifact was marked where both criteria were met. After marking all instances of the BCG artifact, for each EEG channel an average artifact template was calculated over a moving window including 21 artifacts and subtracted from the centre artifact of the moving window in the EEG data.

2.2.5.2 EEGLab

Pulse artifact detection in the ECG channel was performed by adaptive thresholding of the k-teager energy operator, which provides an estimate of the instantaneous frequency content and amplitude of the signal (Mukhopadhyay, Ray 1998). Once the onset of each pulse artifact was marked on the ECG data, the EEG data from each channel was segmented into epochs spanning -0.5s to 1.2s relative to the artifact markers. Then PCA was run on the stacked epochs to find the orthogonal basis functions that captured the most variation in the data. These basis functions defined by PCs were then used to reconstruct the artifact and subtract it from the data. The default number of PCs suggested in the original study (Niazy et al. 2005) and used in most examples of the use of this algorithm is 3 PCs (Debener et al. 2007). However, as I show below the number of PCs required to efficiently reconstruct the artifact can vary widely across different datasets.

2.2.6 Optimization of the artifact removal pipeline

Optimization of the EEGLab artifact removal pipeline involved the choice of enabling ANC at the MR correction stage and the number of PCs used in OBS during the BCG correction. MR correction was run with and without enabling ANC on individual datasets (i.e. individual run). In the BCG correction a wide range of PCs were tested from 3 to 15 with increments of 1, plus 20 and 25 PCs. This resulted in a total number of 30 pipelines for each dataset.

Using a measure (see below) of the EP’s SNR as the evaluation criteria the performance of the pipelines for each stimulus condition was then optimized in two ways. In the first scenario, hereafter referred to as the individual optimization, the pipeline that maximized the SNR for each individual dataset was chosen as the optimal pipeline for that dataset. In the second case,
hereafter referred to as the fix optimization, the average SNR across all datasets was calculated for each pipeline and the pipeline that maximized the average SNR value for the group was selected as the optimal pipeline.

I also investigated possible interactions of the MR gradient and BCG artifact removal steps as implemented in the two software packages. Therefore I tested four possible permutations of the MR gradient and BCG correction algorithms provided in Analyzer-II and EEGLab. This resulted in four pipelines for evaluation per dataset where MR gradient and BCG artifact removal were performed: 1) both in EEGLab with individual optimization 2) both in Analyzer-II, 3) MR gradient correction in EEGLab and BCG removal in Analyzer-II, and 4) MR gradient correction in Analyzer-II and BCG removal in EEGLab with individually optimized number of PCs.

2.2.7 EEG data processing

After removing the MR Gradient and the BCG artifacts, EEG data was filtered using a band-pass Butterworth filter with a high-pass cut-off frequency of 30 Hz. The data was segmented to 1000 ms epochs (from -200ms to 800ms) time locked to the onset of the stimulus. Then the mean signal value in the baseline interval (between -200ms to 0) was subtracted from the epoch. Data from frontal FP1 and FP2 electrodes were used to detect and reject segments with significant eye movements (e.g., blinks) by thresholding data at 100µv. Finally, segments were averaged across all runs for each condition to create ERP waveforms. In order to increase the SNR of the ERPs, EEG signal from a cluster of parieto-occipital (O1, P7, PO7, O2, P8, PO8) and fronto-central (Cz, C1, FC1, C2, FC2) electrodes were further averaged to derive visual and auditory EPs, respectively. Figure 2.2 shows these grand-average auditory and visual EPs across all participants, the defined electrodes and runs, and the corresponding electrode set used in calculation of each EP.

2.2.8 Evaluation criteria

2.2.8.1 SNR measurement

The SNR of the EPs was defined as the peak to peak value of the P1 to N1 peaks for visual EPs, and the N1 to P2 peak for auditory EPs divided by the standard deviation of the baseline. The peak amplitude measurement was performed using a regression based technique (Mayhew et al.
2006), where positive and negative peaks in the evoked response were modeled separately using a general linear model (GLM). For each modality (auditory or visual), each participant’s grand averaged evoked responses across the runs were used to create positive and negative peak segments by manually marking the start and end of the positive and negative peak waveforms respectively. These positive or negative segments were then aligned across participants at their peak locations and averaged to create positive or negative peak templates for the group. The templates were then smoothed with a Gaussian kernel ($\sigma = 5\text{ms}$) and shifted to the original peak latency of the average EP peaks for each participant and run. Averaged EPs from each run were
projected through the GLM onto a set of four basis functions including a positive peak template, a negative peak template and their corresponding derivatives to allow latency variations, which

Figure 2.2: Group averaged left/right auditory and visual evoked potentials. Each evoked potential is calculated by averaging signal from a cluster of electrodes as indicated in the picture.
are illustrated in Figure 2.3. The P1, N1 for visual and N1, P2 amplitudes for auditory were measured from the fitted peak waveforms reconstructed from the GLM regressors.

Figure 2.3: Sample peak regressors for auditory evoked potentials. The figure shows peak templates and their corresponding derivatives used in the linear regression model.

2.2.9 Single trial variability

Artifact residuals can be random and vary across occurrences (Niazy et al. 2005). In particular, these variations can largely impact single trial measurements of the evoked responses in simultaneous EEG-fMRI studies. Some level of variation in trial-to-trial response is inevitable in the EEG data. Hence, another criterion used to evaluate the efficiency of artifact removal methods was trial-to-trial variability of the peak to peak amplitude (P1-N1 for visual and N1-P2 for auditory) across trials in each run.

It should be noted that not all the single trial variability is caused by the artifact residuals. In fact, some level of variation in trial-to-trial response is inevitable in the EEG data. Even in the
absence of MR related artifacts, sensory evoked responses recorded outside of the scanner contain significant variability at the single trial level. This is partially due to the low SNR of the sensory evoked responses and partially due to the inherent variability of the brain responses. For the purpose of this study, the variability measure was also calculated on the data recorded outside of the scanner to serve as a reference.

2.2.10 Task detection

An important area of interest in ERP studies is the effect of different task conditions on the brain evoked responses. Hence, the feasibility of extracting task-related information from the sensory evoked responses was used as another criterion to compare the efficiency of the artifact removal methods. To this end, for both right and left visual stimuli, the contralateral and ipsilateral visual evoked responses were averaged in each run (as described in section 2.2.7). The P1 waveform in the contralateral visual responses precedes that of the ipsilateral responses and has larger amplitude (Di Russo et al. 2002). Hence, the difference between the contralateral and ipsilateral P1 amplitude was used to predict the side of the visual stimulus. This resulted in 96 binary prediction tasks across all participants and runs (16 participants x 3 runs x 2 conditions). The prediction results for different pipelines are summarized in Table 2.4 of the results section.

2.2.11 Schimmel’s (±) reference

This measure provides an estimate of the noise in the averaged EP under the stationarity assumption (Schimmel 1967). An averaged epoch is defined by alternate addition and subtraction of the consecutive evoked responses. The resulting epoch will have a zero mean component and the noise resembles that of a regular averaged evoke potential. The (±) reference was calculated over epochs in each run and the root mean square of the averaged (noise) epoch was used to estimate the power of the noise in the averaged evoke response.

2.3 Results

Figure 2.4 shows sample auditory and visual ERPs obtained through AnalyzerII and EEGLab optimized processing pipelines. The comparison of the results of peak detection methods implemented in the two packages are summarized in Table 2.1 and indicate both techniques achieve high and comparable levels of performance. These results also conform with the
previously reported results by Niazy et al., for the peak detection method implemented in EEGlab (Niazy et al. 2005).
Figure 2.4: Visual and auditory evoked potentials for two sample participants. Each column includes ERPs obtained from one run and rows represent different stimulus conditions. The red waveforms represent ERPs achieved by AnalyzerII processing pipeline and the blue waveforms represent EEGlab results with optimization.
Table 2.1: Performance comparison for the peak detection methods implemented in Analyzer-II and EEGlab.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyzer peak detection</td>
<td>98.8%</td>
<td>99.9%</td>
</tr>
<tr>
<td>EEGlab peak detection</td>
<td>99.9%</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

Figure 2.5 illustrates the range of nPC chosen in the individually optimized pipeline compared to the fix pipeline, where the average nPC in the individually optimized pipelines were found to be higher than the fixed pipeline for each condition (p<0.001).

Figure 2.5: Optimal number of PCs in the OBS algorithm for fix (green line) vs individually (yellow box plots) optimized pipelines. The box-bar plots illustrate the range of optimal PC number (nPC) across different runs and participants for each condition. The green dash to the left shows the nPC selected by the fix optimization process for comparison.
A comparison of the SNR and nPC of the individually optimized pipeline with and without ANC is provided in Figure 2.6. Results from the paired t-test revealed that including the ANC in the pipeline resulted in an increase in the SNR across all conditions (p<0.001). However, no significant effect on the nPC was observed. Overall, out of 192 individually optimized pipeline (16 participants x 3 runs x 4 stimuli), the ANC filter was included in 150 (78%) of the pipelines.

Figure 2.7 shows a comparison of SNR values for different methods and optimization approaches. The results from paired t-tests of the SNR values of different pairs of pipelines shown in Figure 2.7 and their significance after Bonferroni correction are summarized in Table 2.2.
Figure 2.6: Effect of using the adaptive noise cancellation (ANC) filter in EEGLab on the SNR and nPC. Including the ANC in the pipeline resulted in a slight increase in the SNR but no significant effect on the nPC was observed.
Table 2.2: Mean SNR difference values (column – row) of pipelines from Analyzer-II, EEGlab with three versions of optimal basis selection (OBS: 3PC, fix Opt, Ind Opt), and outside scanner recording (No MR). The upper half of the table (blue shade) shows mean SNR differences for visual evoked potentials and the lower half (purple shade) shows mean SNR differences for auditory evoked potentials. The statistical significance of each value is indicated as *p<0.005, **p<0.001, ***p<0.0001.

<table>
<thead>
<tr>
<th></th>
<th>Analyzer-II</th>
<th>EEGlab 3PC</th>
<th>EEGlab fix Opt</th>
<th>EEGlab Ind Opt</th>
<th>No MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyzer-II</td>
<td>-1.45</td>
<td>-0.78</td>
<td>2.52***</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>EEGlab 3PC</td>
<td>-0.38</td>
<td>0.68</td>
<td>3.97***</td>
<td>3.3**</td>
<td></td>
</tr>
<tr>
<td>EEGlab fix Opt</td>
<td>-0.67</td>
<td>-0.29</td>
<td>3.3***</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>EEGlab Ind Opt</td>
<td>-3.84***</td>
<td>-3.46***</td>
<td>-3.17***</td>
<td>-0.67</td>
<td></td>
</tr>
<tr>
<td>No MR</td>
<td>-4.70**</td>
<td>-4.33**</td>
<td>-4.04*</td>
<td>-0.86</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.7: Comparison of SNR values for auditory and visual evoked potentials obtained with different correction algorithms. The outside scanner measurement results (no MR) are also provided for comparison. Error bars indicate the standard error of the mean (SEM).
For visual evoked responses, EEGlab with individual optimization of OBS (EEGlab Ind) was the only method that yielded a significant increase in the SNR value for the inside scanner data over all other approaches. Compared to the data recorded outside the scanner, all methods except for EEGlab with the default setting (EEGlab 3PC) resulted in comparable (i.e., not significantly different) SNR values. Similar results were found for the auditory EPs recorded inside the scanner with the individually optimized EEGlab achieving higher SNR values than other denoising approaches. However, in the case of outside scanner recording Analyzer-II SNRs were significantly lower and only the individually optimized EEGlab resulted in comparable SNR values. Figure 2.8 shows a comparison of SNR values for the four permutations of the gradient (MR). The BCG correction algorithms from the two processing packages with the paired t-test results (and their significance after Bonferroni correction) are provided in Table 2.3.

![Figure 2.8: Comparison of SNR values for pipelines generated by combining correction algorithms from Analyzer and EEGlab. The pipelines include: 1) Analyzer-II—both MR correction and BCG correction are performed in algorithms provided in Analyzer-II, 2) EEGlab(MR)+Analyzer-II(BCG)—MR correction performed in EEGlab followed by BCG correction in Analyzer-II, 3) Analyzer(MR)+EEGlab(BCG)—MR correction performed in Analyzer-II followed by individually optimized BCG correction in EEGlab, 4) EEGlab ind—both correction steps were performed in EEGlab with optimized parameters, 5) noMR—dataset recorded outside the scanner.]
Table 2.3: Mean SNR difference values (column – row) of the four pipelines composed by combining MR gradient and BCG correction methods of different packages compared with SNRs recorded outside the scanner. For the EEGLab package, the individually optimized method was selected as the BCG algorithm. The upper half of the table (blue shade) shows mean SNR differences for visual evoked potentials and the lower half (purple shade) shows mean SNR differences for auditory evoked potentials. The statistical significance of each value is indicated as *p<0.005, **p<0.001, ***p<0.0001

<table>
<thead>
<tr>
<th></th>
<th>Analyzer-II</th>
<th>EEGLab(MR) + Analyzer-II(BCG)</th>
<th>Analyzer-II(MR)+ EEGLab(BCG)</th>
<th>EEGLab</th>
<th>No MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyzer-II</td>
<td></td>
<td>-0.39</td>
<td>2.34**</td>
<td>2.52***</td>
<td>1.85</td>
</tr>
<tr>
<td>EEGLab (MR) + Analyzer-II(BCG)</td>
<td>0.07</td>
<td></td>
<td>2.73**</td>
<td>2.90***</td>
<td>2.23</td>
</tr>
<tr>
<td>Analyzer-II(MR)+ EEGLab(BCG)</td>
<td>-2.67**</td>
<td>-2.73**</td>
<td>0.18</td>
<td></td>
<td>-0.49</td>
</tr>
<tr>
<td>EEGLab</td>
<td>-3.83***</td>
<td>-3.90***</td>
<td>-1.17</td>
<td></td>
<td>-0.67</td>
</tr>
<tr>
<td>No MR</td>
<td>-4.70**</td>
<td>-4.77**</td>
<td>-2.04</td>
<td>-0.87</td>
<td></td>
</tr>
</tbody>
</table>

For visual evoked responses the SNR values from all pipelines reached a comparable level with the outside scanner condition with no significance differences. The combination of individually optimized OBS in EEGLab (EEGLab(BCG)) with the MR gradient correction from either packages resulted in significant SNR improvement compared to the other two pipelines using the BCG correction method from Analyzer-II. The differences in the performance of the pipelines using the same BCG correction techniques were not significant. For auditory evoked responses, while no significant difference was found between pipelines with the same BCG correction method, pipelines including the BCG correction from EEGLab achieved significantly higher SNR
values than other combinations. Contrary to visual responses, only these pipelines resulted in SNR levels comparable to outside scanner data while the SNR values from the remaining pipelines (using BCG correction in Analyzer-II) were lower than data from outside the scanner.

To compare the performance of all methods together, and avoid the distributional assumptions of t-tests and analysis of variance (ANOVA), non-parametric testing was also performed using a Friedman rank test on the data in Tables 2 and 3 with the analysis method as the main factor.

As expected the omnibus rank tests were significant for both auditory and visual responses (p<0.0001 in both cases), so I proceeded to post-hoc testing using the Nemenyi test (Nemenyi 1963). The Nemenyi test is the non-parametric counterpart of the Tukey test for ANOVA and calculates the average pair-wise differences in the rankings. The performance of two methods is significantly different if the difference in their average ranking is greater than the critical difference (CD) value calculated as:

\[
CD = q_{\alpha} \sqrt{\frac{k(k+1)}{6N}}
\]  

(2.1)

Where \(k\) is the number of methods to be compared, \(N\) is the number of participants and \(q_{\alpha}\) is the critical value based on studentized range statistics.

Figure 2.9 shows a CD diagram of the mean ranking of visual and auditory SNR values, where the average SNR rankings for the outputs of the different processing pipelines are indicated on the horizontal axis and the CD value used in the comparison is depicted on the top left corner. Pipelines whose average rank difference is less than the CD value are grouped by the bold black line showing that the difference in their performance is non-significant. Without individual optimization no significant difference is found between Analyzer-II and EEGLab (3PC, fix) pipelines. The diagram for the auditory evoked responses matches the results of the multiple paired t-tests performed on the datasets, where the only pipeline that obtains results comparable to the outside scanner dataset is the individually optimized EEGLab pipeline, and the rest of the pipelines do not show any significant difference in the performance. The visual evoked responses
The diagram also conforms with the t-test results with individually optimized EEGLab pipeline having significantly higher rank than the rest of the pipelines. Also, both Analyzer-II and individually optimized EEGLab pipelines are within the CD of the noMR ranking. The only exception between the results of the paired t-test and the CD diagram is the performance of the EEGLab

**Figure 2.9**: Critical difference (CD) diagram for methods illustrated in Figure 2.7, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the best mean SNR performance. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.
pipeline with fix optimization, which shows significant difference from noMR in the CD diagram.

Figure 2.10 shows a CD diagram and mean ranking of the performance of the four pipelines. Pipelines using individually optimised EE Glen with either package’s MR correction have the highest SNR rankings along with noMR and are not significantly different from noMR. These results also show that the overall performance of the pipeline is mostly determined by the efficiency of the BCG artifact removal algorithm with individual participant optimisation producing the best results.

The results of additional validation criteria (single trial variability and the task detection) are provided in Figure 2.11, Figure 2.12 and Table 2.4. Figure 2.11 shows the distribution of the single trial peak-to-peak variance plotted for different task conditions and pipelines with the corresponding CD diagram illustrated in Figure 2.12. For visual evoked responses the performance of both individual and fixed optimized EE Glen pipelines are within the CD of noMR. For auditory evoked responses however, only the individually optimized EE Glen pipeline falls within the CD of outside scanner data.
Figure 2.10: Critical difference (CD) diagram for methods illustrated in Figure 6, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the best mean SNR performance. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.
For the task detection test, the AnalyzerII, EEGlab 3PC and EEGlab-fix pipelines achieved similar performance while with the EEGlab-ind pipeline the accuracy in predicting the side of stimulus was increased by approximately 10%.

Table 2.4: results for task detection using contralateral and ipsilateral P1 amplitude difference.

<table>
<thead>
<tr>
<th></th>
<th>Analyzer-II</th>
<th>EEGlab 3PC</th>
<th>EEGlab fix Opt</th>
<th>EEGlab Ind Opt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task detection accuracy</td>
<td>70%</td>
<td>70%</td>
<td>71%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Figure 2.11: Single trial variability of the peak-to-peak amplitude for different tasks and pipelines.
Figure 2.12: Critical difference (CD) diagram for methods illustrated in Figure 2.11, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 single trial peak-to-peak variability measures. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.
Finally, the results for Schimel measure and the corresponding critical difference diagram are provided in Figure 2.13 and Figure 2.14. They show that the individually optimized pipeline obtains the closest results to the outside scanner measurement.

Figure 2.13: Schimmel’s measure for different EEG processing pipelines across four stimulus conditions.
Figure 2.14: Critical difference (CD) diagram for methods illustrated in Figure 2.13, summarizing results from post-hoc evaluation of Friedman’s rank test with rank 5 the Schimmel’s noise measure. Methods that are not significantly different because their ranks are less than the upper-left CD rank distance for each diagram are connected together by a thick black line.
2.4 Discussion

In this chapter I aimed to find an optimum processing pipeline for removing MR gradient and BCG artifacts from EEG data recorded during fMRI acquisition while focusing on improving the SNR of event-related potentials. To this end I designed a simple sensory paradigm with auditory and visual stimuli and compared the performance of prominent artifact removal algorithms and data processing packages and their combinations. Furthermore, I compared the results of these different pipelines with EEG data recorded outside of the scanner. Based on the results of previous research (Debener et al. 2007, Vanderperren et al. 2010), I chose to compare AAS and OBS methods as implemented in Analyzer-II and EEGLab, respectively.

The AAS technique works by subtracting an average artifact template calculated over a sliding window from individual artifacts. This is however based on the assumption that variations in the BCG artifact are slow enough to be captured by the sliding window. Alternatively the length of the window can be reduced to make it more adaptive to BCG variations. However, this trade-off makes the averaging process less efficient. The OBS method does not make any assumptions on the temporal correlation between adjacent artifacts. Each artifact is individually modeled and corrected using a set of basis functions derived from PCA. The choice of number of PCs in the OBS approach remains a critical parameter for the performance of OBS. The optimal choice for the number of PCs depends on the variability of the BCG artifact throughout the recording session. Variations in the BCG artifact are caused by factors such as participant’s head movement, heart rate variation, position of participant’s head inside the scanner, and the strength of the scanner’s static magnetic field. Some of these factors are in fact specific to each participant and dataset. Furthermore, the power and structure of the BCG artifact can vary greatly across different channels in every participant (Assecondi et al. 2010, Skrandies 1990). Thus, I hypothesized that individually tuning the number of PCs used in the OBS artifact removal approach can improve the quality of the resulting EEG data.

I evaluated optimizing the number of PCs using two different approaches, using the SNR values of the EPs as the evaluation criteria. In the first approach, as implemented in Vanderperren et al.,
(2010), using EEGLab the number of PCs was chosen to maximize the average SNR value across all participants (i.e., fix optimization). Our results from this approach conform with those of Vanderperren et al., who found no significant effect from the number of PCs on the SNR compared to using the default number of PCs (i.e., 3 PCs). In individual optimization, the number of PCs for each run from each participant was optimized individually. The results of this approach show a significant increase in the SNR values for all four conditions. In fact, the individually optimized OBS is the only method that obtains a SNR comparable to outside scanner measurements preceded by either MR artifact correction algorithms from Analyzer-II or EEGLab. The main improvement in the SNR for the OBS method comes from tuning the number of PCs for individual dataset. As it is illustrated in the critical difference diagrams in Figure 2.9, without individual optimization no significant difference was found between Analyzer (AAS) and EEGLab (3PC,fix) pipelines.

In both optimization approach (i.e., fix and individual) the optimal nPC for retrieving visual evoked responses was higher compared to auditory responses. This can be due to higher amplitude of the BCG artifact in the occipital electrodes compared to the central electrodes and higher degree of head motion in the occipital areas.

Another factor included in the optimization of the EEGLab pipeline was the use of an ANC filter. The ANC filter was included as a part of the fix optimized pipeline and turned on and off in the individually optimized pipeline. While most participants benefitted from the procedure, in some cases the filtering can overcorrect the data and reduce the ERP amplitude.

In the second analysis I tested combinations of MR gradient and BCG artifact correction algorithms from the two software packages. This enabled the study of possible interactions between the MR gradient artifact removal and BCG artifact removal algorithms as well as comparing the performance of the two BCG correction algorithms (OBS and AAS) on the same MR corrected dataset. I have shown that the SNR performance of the pipeline was mostly driven by the choice of the BCG correction algorithm and the pipelines including the individually optimized OBS result in SNR values comparable to outside scanner data.

While no significant effect from the stimulus laterality was observed on the SNR values, the loss of SNR between inside and outside scanner recording was greater for auditory EPs. This could
be due to the difference in the characteristics of both MR gradient and BCG artifacts across different channels as well as the attenuated auditory N1 amplitude recorded inside the scanner, which has been reported in previous studies (Mulert et al. 2005).

In conclusion, our results highlight the importance of considering between participant variability and heterogeneity in choosing the EEG artifact removal method and parameter settings. They also provide a systematic evaluation of two of the most conventionally used EEG artifact removal software packages.
Chapter 3  : Univariate Analysis of Evoked BOLD and EEG Responses

3.1 Introduction

Event-related potentials (ERPs) have been widely used to examine the timing of distributed brain processes involved in perception and cognition. A major question in EEG data analysis is how to localize the neural generators within the brain that are responsible for the distribution of scalp electrical potentials seen in ERPs. As discussed in Chapter 1, the answer to this question involves solving the inverse source localization problem, which is an ill-posed problem because many different source distributions can result in the same scalp potential topography. Furthermore, EEG-based source localization approaches suffer from low spatial resolution (~ 3-5 cm), with an increased likelihood of inaccuracy for deeper subcortical brain structures (Snyder, Raichle 2010).

Prior to the emergence of EEG-fMRI, a large number of studies have aimed at separating sources of different visual evoked potential (VEP) components. While the earlier visual C1 component is generally agreed to originate from the primary visual cortex (see Figure 1.3 for an illustration of VEP components) localizing sources of later VEP components has proved to be more challenging. From a technical viewpoint, these difficulties can be attributed to the low spatial resolution of EEG and differences in stimuli used in paradigms. From a neurological viewpoint, individual differences in the position and extent of the striate cortex as well as temporally and spatially overlapping generators of VEP components that accumulate in the subsequent stages of visual processing all contribute to source localization challenges.

The visual P1 component is generally thought to have origins in the extra striate cortex (BA 18,BA19). However, a number studies have reported overlapping sources for visual C1 and P1 in the striate cortex (Di Russo et al. 2002). These authors also reported extrastriate sources for
posterior N1 and localized anterior N1 to higher cognitive areas in the parietal lobes. Another study by the same group (Di Russo, Martinez & Hillyard 2003) investigated sources of event-related cortical activity during a visual spatial attention task and found sources for the N1 component localized to the primary visual cortex (V1) that were modulated with attention. However, whether primary visual areas such as V1 are affected by attention has been a subject of debate (Mulert 2010).

Since the introduction of EEG-fMRI many studies have attempted to use the concurrent acquisition approach to identify the location of neural generators of different ERP components. For example, Horovitz et al., conducted an EEG-informed fMRI analysis to examine BOLD correlates for N1 amplitude modulation due to changes in image noise levels (Horovitz et al. 2004). Their results suggest neural generators contributing to the visual N1 component in the Fusiform Gyrus. In a spatial attention task, Novitsky et al., used a single trial analysis to study sources of visual P1 and N1 components (Novitskiy et al. 2011). However, the event-related regressors used in their fMRI analysis reflected only the laterality of the response and did not directly correspond to visual evoked response components. Their results revealed overlapping sources for inter-hemisphere differences in P1 and N1 amplitude in the contralateral temporo-parietal junctions. In the same line, a study by Fuglø et al., aimed at distinguishing sources of visual P1 and N1 potentials using checkerboard stimuli. However, once the response from the boxbar regressor was removed, no significant relationship between VEP amplitude and BOLD signal remained (Fuglø et al. 2012).

In the auditory domain, Scarff et al., adopted an interleaved acquisition protocol to examine the anatomical sources of the N1 generators (Scarff et al. 2004) (see Figure 1.4 for an illustration of auditory evoked potential components). While the mean dipole locations from the source reconstruction analysis overlapped with the centre of gravity of the BOLD response in the horizontal plane, the authors reported mismatches in the axial location of the mean equivalent dipole and fMRI activity as well as unmatched asymmetrical fMRI activation patterns. Among studies that have applied a continuous EEG-fMRI recording protocol, Mulert et al., reported that both the amplitude of the auditory N1 component and the BOLD signal in the primary auditory cortex were modulated by the sound intensity level, and positively correlated with each other (Mulert et al. 2005). A single trial analysis of the EEG and fMRI auditory responses by Mayhew
et al., revealed no significant correlations between N1 or P2 amplitudes with the BOLD signal in the primary auditory area. However the authors did report a correlation at the group level between N1 amplitude and the BOLD response in bilateral auditory cortices (Mayhew et al. 2010).

Overall, the earlier sensory components of the auditory and visual potentials are understudied compared to later cognitive components (e.g., P3, MMN) in the EEG-fMRI literature and there is a lack of consensus when it comes to distinguishing sources of individual components. As mentioned above, this may be in part due to differences in the experimental paradigms, stimuli and acquisition protocols. Anatomical variations in participants can also play a role particularly when group level analyses are performed on small areas such as primary auditory and visual cortices (Mulert et al. 2005). Moreover, the sources that influence the BOLD signal variability at the within-participant level are not necessarily the same as those at the between-participant level. However, in most of the existing literature the within- and between-participant effects are intertwined. Finally, the majority of the previously reported results are derived using asymmetrical integration approaches, where information from one modality is used as a prior in the analysis of the data from the other modality. These approaches are based on the assumption that the extent of the response recorded in both modalities overlaps in space and time. However, as discussed in Chapter 1 such assumptions do not always hold. This chapter presents a symmetrical and independent analysis of data from the two modalities to localize sources of distinct components of evoked auditory and visual potentials. Using a robust regression model, the ERP-BOLD relationship is examined at two distinct levels: between- and within-participant. Finally, to reduce anatomical variability across participants in location and extent of the auditory and visual cortices, these areas were individually defined using cortical segmentation results for individual participants.

3.2 Methods

A description of the experimental paradigm, stimuli, participants and recording parameters was provided in the previous chapter. The results provided in this chapter are based on analysis from participants from the first two phases of the recruitment (N = 16). This chapter covers technical considerations relevant to EEG-fMRI experiment designs and discusses the stimulus timing sequence as well as basics of fMRI preprocessing and statistical analysis.
3.2.1 FMRI preprocessing

Analysis of fMRI data presented in this thesis was performed using “Analysis of Functional Neuroimaging” (AFNI v2011_12_21_1014) software package (Cox 1996). Figure 3.1 illustrates a flow chart of the fMRI preprocessing steps used in this work. Below a brief description of these steps will be provided in the same order they were applied to the data.

**Spike removal:** Sudden head movements cause abrupt changes, or spikes, in the BOLD signal, which can interfere with subsequent processing and analysis steps. Using the 3dDespike function, data segments containing abrupt changes in the BOLD signal value were detected and interpolated. The spikes were detected by fitting a smooth curve to individual voxels’ time courses (using an L1 norm) and searching for time points where the fit residual exceed 2.5 standard deviations. The spike values in the interval \([2.5\sigma, \infty)\) were then mapped to \([2.5\sigma, 4\sigma]\). This gradual mapping ensures that the despiked voxels’ time series are a continuous function of the data with bounded distribution tails. Moreover, despiking is shown to improve the performance of the following preprocessing steps (Jo et al. 2013).

**Physiological noise correction:** Physiological noise caused by heartbeat and respiration can seriously confound the fMRI signal. Cardiac and respiratory signals were measured during fMRI acquisition using a photoplethysmograph and a respiratory cushion, respectively, to be used in the correction process. Physiological noise correction was performed using the 3dretroicor program, which uses a slightly modified version of the algorithm introduced by Glover et al., (2000). This correction algorithm fits a low-order Fourier series to the data based on reordering the timing of each scanned volume relative to the phase of the cardiac and respiratory cycles. The fitted Fourier series is then regressed out to remove the physiological confounds in the data (Glover, Li & Ress 2000).
Figure 3.1: Block diagram of fMRI processing pipeline
**Slice timing correction:** In EPI scans, each volume scan is acquired by collecting a sequence of 2D images, or slices. This leads to slice acquisition delays between individual slices within each volume, which can add up to significant temporal shifts between the expected and measured hemodynamic response. The delays in slice acquisition can undermine the reliability and sensitivity of the measured hemodynamic response, particularly in event-related experiment designs. Consequently, to compensate for slice acquisition delays, slice timing correction has been proposed as a preprocessing step in fMRI data (Henson et al. 1999, Calhoun, Golay & Pearlson 2000). During slice timing correction, slices of the same brain volume are temporally interpolated to a reference slice in the volume to account for differences in the acquisition times. The slice timing correction procedure in AFNI is the program 3dTshift. It estimates a new voxel time series from the input dataset so that the slices from a single volume are aligned to the same temporal origin.

**Rigid head motion correction:** A large proportion of the variance in fMRI time series can be attributed to head motion. Changes in the participant’s head position during image acquisition result in the same voxels sampling different regions of the brain. Also, head motion inside the magnetic field causes inhomogeneities in the field that lead to transient artifacts. The former source of artifact is dealt with by using the AFNI 3dvolreg program (Cox, Jesmanowicz 1999). This program corrects for small head movements (i.e., motions of a few mm and rotations of a few degrees) by spatially aligning 3D volume images to a reference image. The alignment is performed by estimating a set of motion parameters (roll, pitch, yaw, x, y, z) that minimize the least-square distance with a chosen reference image in the time series. Furthermore, a max-displacement measure was calculated by 3dvolreg at this stage (defined as the maximum voxel-wise displacement in the xyz space relative to the base volume) and was used to exclude runs with large head motion. Based on this criterion, data from one participant was removed from the analysis provided in this chapter due to high head motion (max displacement > 3mm).

**Time course normalization:** The BOLD signal value can vary substantially between voxels and participants. This is due to variations in physical and physiological noise during the scan as well as physiological difference across participants. This issue constitutes a problem particularly for multi-participant studies, since the signal level may vary greatly at corresponding voxels across participants. In order to achieve better comparison of the BOLD response across voxels and
participants, raw fMRI data was transformed to percent signal change by subtracting the time series mean per voxel and dividing each voxel’s time course values by the mean value.

**Spatial smoothing:** The primary reason for spatial smoothing in fMRI data is to increase SNR. The common approach to reduce the spatial noise in fMRI data is through application of a Gaussian kernel to perform spatial filtering. While the optimum full width half maximum (FWHM) of the filter depends on factors such as the initial SNR level, spatial extent of the activation area and imaging resolution, evidence suggest that for cortical areas a 6mm FWHM filter provides good sensitivity (Hopfinger et al. 2000). In this work, spatial smoothing of the fMRI data was performed using 3dBLURToFWHM function. This function blurs the input dataset until it (approximately) reaches the specified FWHM smoothness, regardless of the data’s original smoothness level.

### 3.2.2 GLM Data Analysis

The General linear model was applied to the data to extract voxels whose time-course significantly co-varied with the stimuli and to generate statistical parametric maps (SPM). GLM is the most commonly used univariate technique in analysis of fMRI data. The analysis model consists of a set of linear equations expressing the fMRI signal time-course as a weighted sum of linear terms representing the effects of interest and confounds. The principal equation of GLM can be stated as

\[
Y = X\beta + \epsilon
\]  
(3.1)

Where \(Y\) is the fMRI data matrix (time x voxels), \(X\) is the design matrix (time x effects of interest and confounds) containing task-related as well as nuisance regressors, \(\beta\) contains the weights for all the regressors in the design matrix (effects of interest and confounds x voxels), and \(\epsilon\) represents the residual error. The GLM attempts to find a set of experimental parameters (\(\beta\)) for a design matrix (\(X\)) that best accounts for the original data (\(Y\)) by minimizing the
unexplained error (ε) in the least square sense. In an ordinary least square (OLS) regression, these weights can easily be calculated as:

$$\hat{\beta} = (X^TX)^{-1}X^TY$$ \hspace{1cm} 3.2

In order to mimic the effect of the brain’s neurophysiological response on the input, the regressors in the design matrix are convolved with a standard hemodynamic response function (HRF) prior to estimating the weight matrix. The HRF model used in this work was a canonical gamma function defined as:

$$H(p, q) = \left(\frac{t}{pq}\right)p e^{p \frac{t}{q}}$$ \hspace{1cm} 3.3

The function has a maximum value of one, which occurs at p*q. Setting $p=8.6$ and $q=0.547$ results in a peak latency of approximately 5s, which mimics the behavior of the natural HRF. The variability of the estimated weights across voxels provides localizing information. To convert the estimated β weights into interpretable statistics, a significance test (usually a t-test) is performed at every voxel. In the statistical analysis of the weights, β weights are divided by the estimated variance at every voxel, resulting in T statistics. These voxel-wise statistics parameter maps (SPMs). To determine voxels with statistically significant T values and reduce the number of false positive activation (i.e. type I error), a threshold (e.g. 0.05, 0.001) is applied to the SPMs and only voxels with an error probability below the threshold are considered significant. However, this approach gives rise to what is known as “multiple comparison problem.” While the false positive error rate for the individual voxel statistical test may seem small, repeating the test for a large number of voxels (which is typically many thousands in fMRI data sets) leads to an increase in the total number of false positive voxels. In other words, the greater the number of statistical tests, the greater the chance of false-positive results. In a given dataset with random noise, the probability of having no false-positive results for $N$ statistical tests are given by

$$p(\text{no false positive}) = (1 - \alpha)^N$$ \hspace{1cm} 3.4

Where $\alpha$ is the false-positive probability in an individual statistical test. One of the solutions to overcome the multiple comparison problem is to control the false discovery rate (FDR) (Genovese, Lazar & Nichols 2002). FDR describes the probability of having at least one false
positive result given the set of reported positive results. This is achieved by sorting voxel-wise statistical test results in ascending order (i.e. from most likely significant to least likely significant).

\[ p_1 \leq p_2 \leq \cdots \leq p_N \]  \hspace{1cm} 3.5

Where \( p_i \) denotes the individual voxel’s type I error probability. For a given FDR threshold of \( q \) (\( 0 < q < 1 \)), the algorithm starts from the first voxel (\( p_1 \)) and searches for the largest \( p_i \) value where:

\[ p_i \leq \frac{iq}{N} \]  \hspace{1cm} 3.6

Then \( p_i \) is the corrected significance threshold corresponding to FDR<\( q \) and all voxels ranked from \( p_1 \) to \( p_i \) are considered significant.

### 3.2.3 Experiment design

An optimal design for simultaneous EEG –fMRI should ideally match with optimal design criteria of both EEG and fMRI experiments. An important factor in both EEG and fMRI experiment design is the time between two successive stimuli, or interstimulus interval (ISI). ERP experimental designs can include ISIs as short as one second to allow for more trials and higher averaged signal to noise ratios (SNRs) in a given time period. However, an ideal event-related fMRI experiment design requires a much longer ISI to prevent overlapping of successive hemodynamic response functions (HRFs), which extend for > 10 seconds. Moreover, such an event-related fMRI design is very inefficient for univariate analysis and requires very long acquisition times to record a sufficient number of trials. The efficiency of a design depends on its ability to achieve the maximum effect size with the smallest number of trials possible. One of the key factors that has been explored to improve the efficiency of the designs is the ISI. As an alternative approach to event-related designs with constant ISI, Dale et al., proposed to present stimuli with randomized ISI (Dale 1999). In this design approach, which is also known as “rapid event-related” design, the ISI between conditions is short enough to cause potential overlap of the HRF for consecutive stimuli. This method relies on the HRF linearity assumption, which implies overlapping HRFs from successive stimuli are linearly superimposed. However, if the
ISI is properly jittered or randomized from trial-to-trial, the contribution of each condition's HRF can be determined through a deconvolution modeling process. Previous studies have evaluated the efficiency of rapid event-related designs (Dale 1999, Liu, Frank 2004) and reported detection power almost as good as those of block design while also having optimal estimation power for the peak and shape of the HRF. Moreover, rapid event-related designs provide additional advantages compared to standard event-related designs. Due to their randomized design, rapid event-related paradigms are highly resistant to habituation and expectation, resulting in a design that is psychologically optimal.

Another advantageous property of randomized ISIs is that successive regressors of the GLM design matrix are relatively uncorrelated. When the regressors for different stimulus conditions are correlated (i.e. collinear) the reliability of the GLM is undermined as the variances explained by each regressor becomes confused with variance associated with another. From a mathematical point of view, in the case of collinearity the design matrix \( X \) is no longer full rank. As a result the \( (X^TX)^{-1} \) term in equation 3.2 becomes unstable, which makes the \( \beta \) estimates inaccurate.

Hence, by randomizing the ISI the design becomes more robust to collinearity. Finally, the flexible timing allows for inclusion of EEG experimental design criteria. The efficiency afforded by variable ISIs allows for a larger number of trials in a defined experiment time, which is critical for achieving good SNR for the ERP response.

The experiment design applied in this study was a rapid event-related paradigm that included four stimulus conditions. The sequence of stimulus presentation was designed using Optseq2 software package (Dale 1999, Dale, Greve & Burock 1999). Optseq2 is a tool for automatically scheduling events for rapid event-related fMRI experiments. The program samples the space of possible random sequences and selects the most efficient sequence. The sequence used in this experiment was designed to optimize the efficiency as the cost function:

\[
\text{eff} = \frac{1}{\text{trace}(C(X^TX)^{-1}C^T)}
\]  

(3.7)
Where \( X \) is the GLM design matrix and \( C \) is the stimuli contrast matrix. In this case each column of \( C \) was a binary vector with “1” in the corresponding index for each stimulus condition (i.e. left visual, right visual, left auditory and right auditory).

3.2.4  Single-trial fMRI response estimation

To evaluate the relationship between the BOLD and ERPs’ components at the single participant level estimates of individual trial responses in both modalities are required. The regression-based peak measurement technique that was introduced in the previous chapter can be applied to single-trial ERPs as well.

Estimating trial-specific responses is a straightforward task in block design or standard (slow) event-related design experiments. For block design paradigms a representative summary image can be obtained by averaging over task blocks or specific time points within a task (Huettel 2009). For standard event-related designs, single trial estimation can be performed through a GLM model, where each trial is modeled by a separate HRF regressor in \( X \) (Rissman, Gazzaley & D'Esposito 2004). However, this approach becomes unstable and inefficient for rapid event-related designs. The small ISI in rapid event-related designs increase correlation values between trial specific regressors despite randomization. This collinearity caused by closely spaced adjacent trials renders individual trial estimates highly variable and unstable. In addition, each extra column in \( X \) reduces the degrees of freedom of the model leading to relatively inefficient parameter estimation for \( \beta \). In a systematic evaluation of proposed techniques for rapid event-related trial estimation, Mumford et al., compared the performance of eight different models on simulated and real data sets and concluded that among the tested methods, the Least Square-Separate (LSS) (Turner 2010) provided a fast and efficient estimate for single trials in rapid event-related designs (Mumford et al. 2012). Based on their results and more recent studies (Abdulrahman, Henson 2016), the LSS method was selected to perform individual trial estimation in this study. LSS runs a separate GLM for each trial where the trial is modeled as the regressor of interest and all other trials are combined into a single nuisance regressor. Since the trial of interest will not be highly correlated with the nuisance regressor, the collinearity problem
is greatly reduced in this model although the $\beta$ estimates remain inefficient since a separate parameter is still estimated for each trial.

The LSS analysis in this study was performed using the AFNI 3dLSS function. Individual trial estimates were calculated for each stimulus condition and averaged across all voxels within an ROI. This resulted in a time course of individual trial estimates for each stimulus condition and ROI.

### 3.2.5 Free surfer and ROI generation

To reduce the impact of anatomical variations between participants, bilateral auditory and visual cortices the ROIs were defined separately for each participant using the cortical segmentation results from FreeSurfer (v5.1.0, [http://surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)). Briefly, the Freesurfer processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002; Fischl et al., 2004a), intensity normalization (Sled et al., 1998), tessellation of the gray matter and white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999a), registration to a spherical atlas that is based on individual cortical folding patterns to match cortical geometry across participants (Fischl et al., 1999b), and parcellation of the cerebral cortex into units with respect to gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004b).

In the first level of analysis, four ROIs were defined to represent the left and right visual and auditory cortices for each participant (hereafter referred to as full ROIs). Subsequently, the visual and auditory ROIs were subdivided into more refined ROIs as illustrated in Figure 3.2. The smaller ROIs were created using anatomically labeled cortical segments available in FreeSurfer. The ROIs defined within the visual area included the primary visual cortex V1 (Brodmann Area
visual areas V2 (BA18) and V3 (BA19) in the extrastriate cortex and the area MT. The auditory ROIs consisted of primary auditory cortex A1 (BA41, BA42), planum polare A2, planum temporale A3 (superior portion of BA22) and lateral superior temporal gyrus A4 (lateral and anterior BA22). For each participant four sets of ROIs were created in the left and right auditory and visual areas.

Each ROI set was used as a mask to divide the activation for each stimulus condition into sub-regions within the auditory or visual cortices. An FDR threshold of 0.05 was applied to SPM values in each ROI to correct for multiple comparisons. Voxels within each ROI that passed the FDR thresholding were used to sample and average the GLM regressor coefficients (β) for the corresponding ROI. This resulted in four averaged ROI values for each stimulus condition per participant per run. The average β value in each ROI was then used as the fMRI feature in a robust regression with ERP features.

3.2.6 Robust regression

Despite its ease of implementation (see 3.1, 3.2), the OLS regressor is extremely sensitive to outliers (i.e., observations that are quite far from the major distribution in the data). Since the model assumes a normal distribution of the errors, its performance is drastically affected by the outliers. Unlike the OLS regression, in robust regression the performance of the method is not

Figure 3.2: Visual and Auditory ROIs for a sample participant: a) Auditory ROIs. b) Visual ROIs from the left and right view. The inflated brain surfaces are created using SUMA software packages.
sensitive to outliers. Such robustness is achieved by assigning different weights to different data points in the calculation of the model, thus reducing the influence of the outliers on the regression estimates. A robust estimator can be evaluated in terms of its breakdown point and efficiency. The breakdown point of an estimator determines the resistance of the estimator in the presence of outliers and is defined as the smallest percentage of the outlying samples that will cause the estimator to break down and fail to extract the main underlying distribution of the data. The efficiency of the estimator is defined as the ratio of its minimum theoretical variance to its actual variance (Andersen 2008). In the context of regression, relative efficiency of the estimators are calculated as the ratio between its mean-squared error to that of the least-square estimator (Stuart 2011). The robust regressor used in this work was an MM-estimator, which combines a high break down point with good efficiency. It provides a 50% breakdown point and 95% asymptotic efficiency for normal errors. Additionally, the robust estimator identifies and excludes outliers from the regression.

The algorithm used here is based on the methods described by Yohai et al., (Yohai 1987) and Koller and Stahel (Koller, Stahel 2011). These methods are implemented in the “Robustbase” statistics package in R.

3.2.7 Analysis of EEG data

The analysis of EEG data for this chapter was performed in EEGLab. The initial steps of EEG data analysis consisted of MR gradient and BCG artifact correction (see Chapter 2). MR gradient artifact correction was performed using Fmrib FASTR EEGLab plug-in. The parameters of correction were similar to what was described in Chapter 2 with adaptive noise cancellation (ANC) filter enabled. For BCG correction the optimal basis selection (OBS) algorithm with the optimization process described in Chapter 2 was applied to the data. EEG data was then bandpass filtered from 0.6Hz to 40Hz to reduce low frequency drifts and high frequency noise. A 90% trimmed standard deviation (TSTD) was calculated for individual channel time courses and channels where the TSTD exceeded 3 standard deviation of TSTD across all channels were marked noisy channels. To further improve the SNR of the evoked responses independent component analysis (ICA) was used to correct for ocular artifacts. To reduce the impact of noisy channels and data segments on the ICA decomposition, these channels were excluded from the calculation of ICA weighting matrix. Once the ICA weighting matrix was calculated artifact
related ICs were detected and removed from the data using the ADJUST algorithm (Mognon et al. 2011). ADJUST provides an automated approach for detection of artifact related ICs by combining temporal and spatial stereotyped artifact-specific features. These features are optimized to capture ocular artifacts and general discontinuities in the data. The application of ICA ocular artifact correction enables retaining more data (and consequently more trials) for averaging. Increasing the number of trials is also particularly beneficial for within participant analyses. After removal of artifact related ICs, the channels that were initially excluded from the ICA decomposition were interpolated from the adjacent channels using spherical interpolation. Next, a common reference channel was calculated by averaging all channels (excluding the ECG) channel and data from all channels were re-referenced to the new common-average channel. Data segments were then created from [-200ms, 800ms] relative to the stimulus onset and segments containing extreme values (beyond ± 100µv) were eliminated. Trials for each stimulus type were then averaged over a cluster of electrodes (see Figure 2.2) to create ERPs.

### 3.2.8 Feature evaluation and regression analysis

Instead of using asymmetrical integration approaches such as EEG-informed fMRI (where EEG driven regressors are used to predict fMRI activation) or fMRI-informed EEG (where fMRI analysis results are used as constraints in EEG source modeling), a symmetrical analysis was performed by applying robust regression on features calculated independently in each modality.

From the EEG data, three peak values were measured for each type of stimulus: For visual stimuli, the amplitude of the visual P1 (positive peak between 80-110 ms post stimulus), N1 (negative peak 140-180ms post stimulus) and the peak-to-peak value (P1-N1) were extracted. For the auditory stimuli amplitude the auditory N1 (negative peak 90-120 ms post stimulus), P2 (250-350 ms post stimulus), and N1-P2 were used. In order to account for the noise in the ERPs and low frequency/baseline effects, the SNR ratio of each peak was used instead of the peak amplitude. The peak SNR was defined as the peak amplitude (for P1, N1 or P2 peaks) or the peak-to-peak amplitude (for P1-N1 and N1-P2) divided by the standard deviation of the baseline. The baseline was defined as the [-200 0] ms segment of the EEG signal relative to the stimulus onset.
In each analysis step, the peak SNRs of the EPs were regressed against the amplitudes of the HRF using the MM-estimator. Both ERP and BOLD features were normalized (divided by the standard deviation) to have both sets of values on comparable scale and make regression results comparable across plots. Hence the slope of the regression represents the correlation between ERP and BOLD values. The strength of the relationship was evaluated by calculating the slope of the fitted line and the significance value associated with it as well as robust residual standard error.

The regression analysis was performed on three levels: In the first level, fMRI and EEG features were averaged across all runs for each participant. For each participant, fMRI features consisted of the average β values in the FDR-thresholded auditory/visual ROIs per run, averaged across three runs. The ERP features consisted of peak measurements on the averaged ERP per run, averaged across three runs.

In the second level, visual and auditory ROIs were divided into sub-ROIs, as described above, and for each participant the average β values were calculated in individual sub-ROIs and across three runs. The ERP features remained the same as the previous level (i.e., peak measurements on the averaged ERP per run averaged across runs). The aim of this level of analysis was to examine the visual and auditory cortices at finer resolution and determine whether sources of individual ERP components are more likely to be related to any of the anatomically defined sub-ROIs.

Finally, in the third level of analysis the top 50% of the participants who showed higher SNR values in the EEG data and stronger fMRI activations were selected for a within participant analysis. Single trial ERP and fMRI responses from each participant were sorted based on the amplitude of the fMRI response and divided into four equal sized bins covering the minimum to maximum amplitude values. ERP and BOLD measures associated with trials in each bin were averaged together and the average ERP and BOLD values across the bins were plotted against each other. This process was performed for each sub-ROI of the visual/auditory cortex and each ERP peak.
3.3 Results

The SPMs obtained by GLM analysis for a sample participant is provided in Figure 3.3 and demonstrate contralateral response to sensory stimuli in auditory and visual cortices. Figure 3.4 shows the between participant regression results for the first level of the analysis, where data from all runs are used to evaluate each point in the plot (i.e., each participant is represented by one point). The corresponding values from the regression analyses are provided in Table 3.1. Two samples were identified as outliers (triangles) in the P1 and P1-N1 plots.

In the visual modality, all BOLD-ERP relationships for all three ERP components had significantly non-zero slopes (p < 0.01). The smallest residual value (i.e., the tightest fit) is found with the P1-N1 measure, followed by the P1 measure. However, the largest absolute regression slope was observed for the P1 measure.

Similarly, in the auditory plots significant relationships were found for all ERP measures with the BOLD response. The residual error values were found to be in the same range for different ERP features and the steepest slope was associated with the N1-P2 measure.

The results for the second level of the analysis of the visual and auditory responses are illustrated in Figure 3.5 to Figure 3.10, with the corresponding numerical result presented in Table 3.1 and Table 3.2.
Figure 3.3: fMRI activation maps for a sample participant. Each row represents SPMs for a stimulus condition with T-values thresholded at P<0.001 (uncorrected).
Figure 3.4 Regression results for visual (left) and auditory (right) ERP components vs BOLD response in the visual/auditory cortex. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.5: Regression results for visual P1 in four ROIs of the visual cortex. Each point on the plots represents the visual P1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.6: Regression results for visual N1 in four ROIs of the visual cortex. Each point on the plots represents the visual N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.7: Regression results for the peak to peak P1-N1 measure in four ROIs of the visual cortex. Each point on the plots represents the visual P1-N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.8: Regression results for the auditory P2 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory P2 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.9: Regression results for the auditory N1 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory N1 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Figure 3.10: Regression results for the auditory N1-P2 SNR in four ROIs of the auditory cortex. Each point on the plots represents the auditory N1-P2 SNR and the average BOLD response in the ROI for one participant. The triangle marker (▲) indicates outlier points detected by the robust regression algorithm.
Table 3.1: Robust regression summary for visual ERP components in the full ROI and individual ROIs. The statistical significance of the slopes are indicated as *p<0.05, **p<0.01, ***p<0.001 after Bonferroni correction.

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>N1</th>
<th>P1-N1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>slope</td>
<td>residual</td>
<td>slope</td>
</tr>
<tr>
<td>Full ROI</td>
<td>0.77**</td>
<td>0.57</td>
<td>-0.74</td>
</tr>
<tr>
<td>V1</td>
<td>0.52</td>
<td>1.04</td>
<td>-0.59</td>
</tr>
<tr>
<td>V2</td>
<td>0.73***</td>
<td>0.57</td>
<td>-0.80***</td>
</tr>
<tr>
<td>V3</td>
<td>0.38</td>
<td>0.74</td>
<td>-0.52</td>
</tr>
<tr>
<td>V4</td>
<td>0.25</td>
<td>0.60</td>
<td>-0.39***</td>
</tr>
</tbody>
</table>

The regression results for the visual sub-ROIs are provided in Table 3.1 for the ERP components. Since the relationships for each of the three ERP peak were tested across five ROIs, the corrected significance level after Bonferroni correction would be 0.003 (0.05/15).

For the visual P1 peak, stronger relationship is observed in area V2 compared to the full ROI. In the remaining sub-ROIs the relationship is weakened in terms of slope, significance level and regression residuals. For the visual N1 peak, the ERP-BOLD relationship was strongest in V2 and V4. For the P1-N1 measure, the full ROI showed the strongest relationship followed by a comparable relationship observed in V2. The next most coherent relationships were found in V4.
Table 3.2: Robust regression summary for auditory ERP components in the full ROI and individual ROIs. The statistical significance of the slopes are indicated as *p<0.05, **p<0.01, ***p<0.001 after Bonferroni correction.

<table>
<thead>
<tr>
<th></th>
<th>P2</th>
<th>N1</th>
<th>N1-P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>slope</td>
<td>residual</td>
<td>slope</td>
</tr>
<tr>
<td>Full ROI</td>
<td>0.88</td>
<td>0.77</td>
<td>-0.62</td>
</tr>
<tr>
<td>A1</td>
<td>0.63*</td>
<td>0.47</td>
<td>-0.70*</td>
</tr>
<tr>
<td>A2</td>
<td>0.27</td>
<td>0.21</td>
<td>-0.17*</td>
</tr>
<tr>
<td>A3</td>
<td>1.05*</td>
<td>0.57</td>
<td>-0.56</td>
</tr>
<tr>
<td>A4</td>
<td>0.17</td>
<td>-</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

The auditory regression results are shown in Table 3.2. For the auditory peak components, the relationship deteriorates in area A4 for all peaks and does not reach significance. The remaining ROIs show different relationships depending on the component. For auditory N1, areas A1 and A2 showed the same significance level, while area A1 demonstrated larger slope. For the P2 component, significant relationships were observed in areas A1 and A3, with a larger slope present in area A3. The N1-P2 measure was found to be most strongly associated with the BOLD values in the full ROI. While, going to sub-ROIs did not cause any significant improvement, comparable relationships were found in A1 and A3.

Figure 3.11 and Figure 3.12 illustrate the within participant relationship for a few representative participants. Each panel in the figures includes plots for one sample participant. The three plots in each panel represent BOLD-ERP relationship across different sub-ROIs. The visual ROI V4 (area MT) and the auditory ROI A2 (planum polare) were excluded from the analysis due to sub-threshold activity in most of the participants. The BOLD-ERP relationship for the remaining three ROIs is depicted in the figures. Each color (red, green or blue) represents the relationship for one ROI. At the within participant level, no significant relationship was observed for any of the visual or auditory modalities.
Figure 3.11: Visual analysis results for sample participants. The horizontal axis represents the averaged single trial BOLD responses (calculated using LSS) for the four bins. The vertical axis represents ERP peak SNR for averaged ERP within each bin. Each panel illustrates the relationship between one ERP peak and the BOLD response. Within each panel, the relationships for individual ROIs are plotted using different colors. The blue curve represents the relationship in area V1, red represents V2 and green represents V3.
Figure 3.12: Auditory analysis results for sample participants. The horizontal axis represents the averaged single trial BOLD responses (calculated using LSS) for the four bins. The vertical axis represents ERP peak SNR for averaged ERP within each bin. Each panel illustrates the relationship between one ERP peak and the BOLD response. Within each panel, the relationships for individual ROIs are plotted using different colors. The blue curve represents the relationship in area A1, red represents A3 and green represents A4.
3.4 Discussion

In this chapter the relationship between different components of the auditory and visual EPs and the BOLD response in auditory and visual cortex was examined. To improve the efficiency of the experiment design, a rapid event-related paradigm was used for stimulus presentation. The improved efficiency of the rapid event-related designs is due to variable ISI of the paradigm and increases with deceasing mean ISI. The decreased mean ISI value not only improves the efficiency due to increased number of trials, but also improves the ability to estimate trial specific activation patterns (Mumford et al. 2012). Finally, the additional flexibility afforded by the variable ISI enables designing a paradigm that satisfies criteria for both EEG and fMRI experiments without sacrificing statistical power or efficiency of either modality.

The majority of existing EEG-fMRI studies on localizing sources of auditory or visual components have used asymmetrical analysis approaches such as using fMRI activations as constraints in EEG source reconstruction or incorporating EEG driven measures as regressors in the fMRI GLM design matrix. As mentioned above, these approaches are based on the assumption of overlapping spatial or temporal responses in EEG and fMRI. However, this assumption is not always met. For instance, highly synchronous neuronal firing in a small cortical patch can result in detectable EEG signal for little metabolic cost and insignificant hemodynamic changes. Conversely, neural activation can lead to generation of BOLD signal, but no detectable EEG signal is generated due to the self-cancelling spatial orientation of the underlying generators (Huster et al. 2012, Nunez, Silberstein 2000). In such circumstances, using data from one modality as a prior to derive the results in the other may lead to a biased analysis.

In this chapter the EEG and fMRI data were analyzed independently and their relationship was evaluated in a post hoc analysis. To enable quantitative evaluation and comparison of the results, a univariate robust regression model was fit to the relationship. The EEG-BOLD relationship was analyzed at two distinct levels: within and between participant.

At the within participant level, no significant relationship was found with BOLD signals for either visual or auditory ERP components. However, this finding on its own is not sufficient to dismiss a relationship between the ERP peaks and the BOLD. The lack of a prominent
relationship in this case may be caused by low SNR and/or lack of a controlled modulation of the stimuli and response in the experimental paradigm.

At the between participant level, while the relationship for some ERP components improved by going from full ROI to sub-ROI analysis, others remain the same or deteriorate. For both visual P1 and N1 peaks the strongest relationships were found in area V2. However, for the visual N1. In ROI V4 (corresponding to area MT), no relationship for the P1 component was found, however the visual N1 component showed a significant relationship with a small slope value. These results are consistent with the previous findings in the literature that suggest sources for P1 in the extrastriate cortex (V2), and for N1 in the extrastriate (V2 and V3) as well as temporoparietal junction (V4) (Di Russo et al. 2002, Novitskiy et al. 2011, Di Russo, Martinez & Hillyard 2003).

The full ROI analysis for the auditory ERP components revealed significant relationship for N1-P2 peak measure. The individual sub-ROI analysis demonstrated the auditory N1 to be more strongly associated with A1, while for auditory P2 the strongest relationship was observed in A3. These findings are consistent with previous reports, which suggest sources for auditory N1 component in the primary and secondary auditory cortex whereas the P2 reflects higher level processes and areas such as planum temoprale (A3). The stronger association of the visual P1-N1 and the auditory N1-P2 with the full ROI conforms with the fact that both these measures are comprised of two peaks and thus correspond to several sources in extended regions of the brain. Due to their relatively higher resilience to noise compared to individual peak measures, the peak-to-peak ERP measures (such as visual P1-N1 or auditory N1-P2) are favorable in the EEG-fMRI. When used in such context, the peak-to-peak measures are often incorporated in a GLM design matrix to represent the enelectrophysiological response and extract the associated BOLD signal (Mayhew et al.2012, Mayhew et al.2013, Fuglo et al. 2012). The abovementioned observation highlights the importance of considering the nature of the relationship between peak-to-peak ERP measures and the BOLD response while interpreting results from such GLM analyses.

The outlier points detected by the robust regression were further inspected retrospectively. In the visual regression plots, the outlier point below the regression line with negative BOLD value
represents data from a participant (P1) with only one run remaining after removing high motion runs. A large number of trials (>30%) were removed for the same participant due to ocular artifacts and excessive eye movement. The remaining outlier points in ROIs V2 and V4 for both P1 and N1 regression plots are located above the regression line, which indicates strong BOLD response. The data from participants corresponding to these outlier points (P12 and P15) showed small head movement and large number of trials (>90%) retained after artifact correction. The mismatch between amplitudes of the ERP and BOLD response for these participants might be due to variations in the spatial distribution of the visual ERPs across the scalp, which leads to inefficient measurement of ERPs. Furthermore, as mentioned before, ERPs represent only the phase-locked portion of the neural evoked response, while time-locked neural responses also contribute to the BOLD signal.

In the auditory results, the outlier points below the regression line are observed in area A2 and correspond to the same participants (P1 and P9) for both auditory N1 and P2 peaks. For these participants a significant portion of auditory trials were eliminated (>40%) due to artifacts. Furthermore, both these participants demonstrated at least one run with large head motion. Similar to the visual regression plots, the outlying data points located above the regression line represent strong BOLD activity, which is not reflected in the ERP response. Such points include the outlying data points in auditory area A1 for the P2 peak (P6, P11, P15), in area A3 for both N1 and P2 peak (P2, P13) and in area A4 for N1 and P2 peak (P2, P11). For all these participants at least 90% of the auditory trials were retained, and none of the participants showed high head motion in any of the runs. Thus the mismatch between ERP and BOLD measures might be attributed to individual variability and limitations of the phase-locked ERP response in studying ERP-BOLD relationship.

In summary, while the relationship for some ERP components improve by going from full ROI to sub-ROI analysis, others remain the same or deteriorate. Furthermore, for all peak measures, significant associations were found in more than one ROI. These observations can be explained by the fact that ERP components may have primary generators in one or more ROIs in the visual/auditory cortex. Also, each ROI may contribute to more than one ERP component. Hence a unique one-to-one relationship between the components and ROIs cannot be established. In addition, the neurofeedback mechanism in the sensory cortices (Di Russo et al. 2002) adds to the
complexity of ERP-BOLD relationships. This suggests that a univariate approach is not the optimal technique to investigate the ERP-BOLD correspondence since the model cannot incorporate the interaction between different ERP components and ROIs.

Another issue with the traditional ERP-BOLD analysis approach is that the averaged ERPs represent only the portion of the neural response that is phase-locked to the stimuli. However, it has been argued that brain responses also include non phase-locked activity, which is manifested across different frequency bands. There has been increasing support in the literature that studying the time-locked response (measured in frequency domain) provides a more comprehensive picture of the brain processes and thus is a more suitable approach for relating evoked task related neural activity to perception and cognition (Siegel, Donner 2010, Kilner et al. 2005, Donner, Siegel 2011).

The proposed analysis method in the following chapter aims to address the abovementioned issues. In Chapter 4 a multivariate technique is adopted to perform a symmetrical integration of the event-related EEG and fMRI responses. Furthermore, instead of the averaged phase-locked ERP responses, the analysis incorporates the time-locked event-related response across multiple frequency bands.
Chapter 4: A Multivariate Approach to Analysis of Simultaneously Recorded Evoked EEG and BOLD fMRI Responses

4.1 Introduction

Simultaneous EEG-fMRI recording is becoming a popular technique in the study of sensory and cognitive functions (Huster et al. 2012). Combining EEG and fMRI enables utilizing the spatial resolution of fMRI to study the dynamics of cortical oscillation patterns. Oscillatory brain activity recorded in human electroencephalogram (EEG) reflects the synchronous activation of neurons in networks across the brain. These oscillations comprise activity over a broad frequency range. The different frequency ranges in the EEG signal are commonly referred to as “bands,” whose definition typically follows clinical EEG conventions: delta (~2–4 Hz), theta (~4–8 Hz), alpha (~8–12 Hz), beta (~12–30 Hz), and gamma (~30–80 Hz)(Donner, Siegel 2011).

Ongoing oscillations can be modulated by the internal brain state (e.g. vigilance, arousal or sleepiness) or external stimulus in sensory, cognitive or motor tasks. In addition to the transient event-related potentials (ERPs), cognitive and sensorimotor processes elicit changes in the oscillatory activity that is time-locked, but not phase-locked, to the event. These task-related changes reflect a decrease or increase in the synchrony of the underlying neuronal populations. The former phenomenon is referred to as event-related desynchronization (ERD), and the latter as event-related synchronization (ERS) (Pfurtscheller, Lopes 1999). The ERD/ERS effects are frequency band specific and thus can occur at the same scalp location simultaneously.

Spectral analysis is the primary method to study the ongoing oscillations of the brain and event-related changes in oscillations. While the traditional method of studying stimulus induced changes in the EEG signal involves extracting the phase-locked response through averaging (i.e., ERPs), recent evidence suggests that spectral analysis is better suited for linking electrophysiological response to perception and cognition (Donner, Siegel 2011).
cortical response often contains sustained modulations that are driven by recurrent network interactions within the brain and thus are not phase-locked to the stimulus (Siegel, Donner 2010, Wyart, Tallon-Baudry 2008). Moreover, many perceptual and cognitive processes such as attention, short-term memory and decision making evolve over time scales longer than ERPs (Siegel, Donner 2010). A major challenge in understanding the precise nature of task-induced changes in neural oscillation is the limited spatial resolution of EEG. Oscillatory activity recorded at the sensor level represents a coarse summation of cortical activity and lacks spatial specificity.

Simultaneous EEG-fMRI provides a suitable platform to investigate brain oscillations by utilizing the high temporal resolution of EEG and spatial resolution of fMRI. Occipital alpha oscillations are the most widely studied rhythms due to their prominence in the EEG data, relevance to cognitive and sensory processes, and ease of measurement (Laufs 2009). EEG-fMRI studies of spontaneous oscillatory activity (in the resting state) have revealed converging evidence suggesting a negative correlation between alpha rhythm and the baseline fluctuations of the Blood oxygen level dependent (BOLD) fMRI signal in the occipital, thalamus and default mode network area(Goldman et al. 2002, Feige et al. 2005, Moosmann et al. 2003, Becker et al. 2011). While there is general consensus on the negative correlation of the alpha band oscillations on the baseline fluctuations of the BOLD signal, the interaction between alpha rhythm (as well as other frequency bands) and task induced BOLD response remains unclear.

In the context of sensory paradigms, which are the focus of this research, pre-stimulus occipital alpha power was shown to co-vary with the amplitude of the visual evoked BOLD response in sub-regions of the visual cortex (Becker et al. 2011, Scheeringa et al. 2011, Mayhew et al. 2013). Becker et al., found that the posterior alpha rhythm accounts for variability in the evoked BOLD response in the visual cortex (Becker et al. 2011). In particular, they observed a negative linear correlation between the pre-stimulus alpha power and the visual BOLD response in extrastriate areas (V2). In contrast, Mayhew et al., reported negative correlation between pre-stimulus alpha power and the visual BOLD response in the primary visual cortex (V1), and parts of the LGN for higher contrast visual stimuli (Mayhew et al. 2013). Despite discrepancies in the discovered sites, results from both studies suggest that the association between alpha power and the visual BOLD response is not uniform across the visual cortex. In fact, the alpha-BOLD association may
vary substantially within the visual cortices and depends on the experimental paradigm. In a similar study, Schreenga et al., found no significant relationship of pre-stimulus alpha power on the fMRI visual response, but instead observed a correspondence between the phase of the alpha rhythm at the stimulus onset and the visual BOLD response (Scheeringa et al. 2011).

Similarly, in the somatosensory and motor area, the relationship between task-induced changes in cortical oscillations and the BOLD response remains unclear. While previous studies have demonstrated a negative correlation between ongoing rolandic alpha and beta oscillations and the baseline fMRI signal during rest (Ritter, Moosmann & Villringer 2009), results from studies that investigated task-induced responses have been less consistent. In an study by Winterer et al., sources of task related changes across different frequency bands measured by MEG were shown to overlap with fMRI activation locales, but no relationship between the magnitude of MEG and BOLD responses were found (Winterer et al. 2007).

In comparison to the visual system, fewer studies have focused on brain oscillations originating from the auditory cortex, and those measuring oscillation have often used steady-state response to a particular rate of stimulation (e.g. 40 Hz). It has been argued that due to the small size of the auditory cortex, oscillatory activity originating in this region results in weaker scalp potentials and is often masked by the more prominent occipital and sensorimotor rhythms (Weisz et al. 2011). While there is enough evidence supporting the existence of an independent auditory alpha rhythm, knowledge about its functional significance, its relationship to task-related responses and its correlation to the BOLD signal remain scarce (Weisz et al. 2011). The majority of EEG-fMRI studies focus on cognitive components of the auditory evoked response (e.g. the auditory P300 wave) using oddball paradigms (Eichele et al. 2005, Liebenthal et al. 2003, Mulert et al. 2004, Bénar et al. 2007, Goldman et al. 2009). There are, however, limited results on the relationship between oscillatory rhythms of the brain and the BOLD sensory response in the auditory domain.

Among the few EEG-fMRI studies that have explored oscillations in the auditory modality, Mayhew et al (Mayhew et al. 2013) reported a correlation between higher levels of occipital alpha power and the relative decrease of BOLD signal in the auditory cortices. In another study
by Walz et al., no relationship between occipital alpha power and the BOLD response in the primary sensory auditory area was found (Walz et al. 2015).

In summary, while there is general agreement on the existence of spatial and temporal correlations between ongoing oscillations and spontaneous BOLD signal fluctuations, the interaction between task related changes in oscillatory activity and their effect on the evoked BOLD response remains unclear for the alpha band within the visual cortex and is largely unstudied for evoked sensory responses outside the visual cortex (e.g., auditory) and for frequency bands other than alpha.

The reasons behind these discrepancies can be multifold. First, common analysis approaches focus on the activity from only one or two frequency bands associated with cognitive or sensory processes. This approach does not provide a complete picture of the underlying oscillatory dynamics elicited by the process since oscillations of different frequencies can coexist and interact with each other, resulting in a wide range of brain states (Siegel, Donner 2010). Second, the functional significance of different frequency bands can vary depending on the measurement site, process and cognitive state (Donner, Siegel 2011, Olbrich et al. 2009). Lastly, the univariate GLM approach does not capture the interaction within or between brain regions or networks, which can be manifest both in EEG oscillations and fMRI responses.

Here I propose a multivariate analysis framework that addresses the above discrepancies. I apply this method to study the relationship between auditory and visual ERD/ERS and the BOLD response in multiple frequency bands and regions of interest (ROIs) in visual and auditory cortices. The proposed framework is based on partial least square (PLS) analysis, which has already proven very useful in the analysis of neuroimaging data (McIntosh, Lobaugh 2004, Krishnan et al. 2011). Due to its ability to handle high dimensional data, the proposed method enables simultaneous analysis of EEG data across multiple frequency bands and channels, and multiple spatial ROIs. Furthermore, the multivariate approach allows extraction of functional connectivity relationships across ROIs and frequency bands and hence provides a more comprehensive image of the underlying oscillatory dynamics that are generated by the stimulus.
4.2 Methods

Data was collected by administering the audiovisual paradigm described in Chapter 2. The results provided in this chapter are based on analysis from participants from all three phases of the recruitment (N = 20). Data from two subjects were removed from further analysis due to excessive head motion (max. displacement > 3mm). The fMRI data processing for this chapter is the same as what was described in Chapter 3. The average β values calculated in visual and auditory ROIs will be used as the fMRI features in this chapter.

The EEG processing was similar to what was performed in Chapter 3, with the exception of the ballistocardiogram (BCG) artifact removal. While the BCG artifact removal in Chapter 3 used individually optimized number of PCs (nPCs) for artifact modeling, in this Chapter the same number of PCs (6 PCs) were used for BCG correction. Since one of the main aims of this Chapter is to investigate variations of the brain response across participants, the same processing pipeline was applied across the group. The chosen nPC value (i.e. 6) was based on the fixed-optimization analysis results from Chapter 2, which indicated this number to be the maximum nPC across different stimulus conditions. The EEG processing steps included MR and BCG artifact correction, bandpass filtering, bad channel detection, ICA artifact removal, bad channel interpolation (see Chapters 2 & 3 for more details on each processing step). These steps were followed by spectral analysis of the EEG data as described below.

To extract the frequency band information from EEG data, a 256 point, short-time Fourier transform with a Hamming window function was performed separately on 500ms pre-stimulus and post-stimulus windows. Individual frequency band powers were calculated by averaging frequency bins of approximately 1Hz in the range of 4-8Hz (theta), 8-12Hz (alpha), 13-20Hz (beta1), 21-30Hz (beta2). ERD/ERS in each frequency band was calculated as the average band power in the pre-stimulus interval minus the post-stimulus interval. For each participant the median ERD/ERS value across all trials was calculated at every electrode channel. Left and right sided responses in each modality (i.e. auditory or visual) were then averaged together to increase the SNR. To preserve the spatial correlation between electrode channels, spatial smoothing was performed on the resulting EEG topographic maps using a two dimensional Gaussian kernel that covered one adjacent electrode in each direction.
4.2.1 Data integration and analysis

4.2.1.1 Partial least square analysis

Partial least square (PLS) is a multivariate statistical technique that extracts common patterns of variance between two datasets. PLS was introduced to the neuroimaging literature by McIntosh et al., and is particularly suited for neuroimaging data applications due to its ability to handle high dimensional data (McIntosh, Lobaugh 2004, McIntosh et al. 1996). Different variations of the PLS method have been adapted for application in neuroimaging data analysis (see (Krishnan et al. 2011) for a full review). The method used in this study is a modified version of the PLS analysis and resampling techniques proposed by(McIntosh, Lobaugh 2004, Krishnan et al. 2011). PLS analyzes the relationship between the matrices \( X \) and \( Y \), which contain measurements collected from the same observation in each row. The structure of \( X \) and \( Y \) data matrices, which contain EEG and fMRI data respectively, is shown in Figure 4.1a. Here, each row of the \( X \) and \( Y \) matrices stores EEG and fMRI feature, measured from the same participant, respectively. For the remaining 18 participants the \( X \) matrix (18x252) contains ERD values measured across electrode channels (excluding the ECG channel) and frequency bands (4x63=252). Within each frequency band, the mean value across channels was subtracted and values in the four bands were concatenated to form one row of the EEG data matrix. The \( Y \) matrix (18x4) contained participants’ average BOLD response for each of four ROIs. Similarly, each row of the fMRI data matrix included BOLD responses in four ROIs, averaged for left and right sided stimuli. While the conventional approach in PLS analysis is to normalize the variables to create a cross-correlation matrix, in this analysis, in order to preserve the topography of power distribution within each frequency band the EEG (and fMRI) data matrix was only mean centered. Hence, the \( X \) and \( Y \) notation in the following equations refer to mean centered data matrices.
Figure 4.1: Block diagram of the input data matrices and the leave-one-out PLS framework. a) Structure of the X and Y input matrices for the PLS analysis. Each row of the X matrix contains frequency band values across all electrode channels for one participant. The corresponding row in the Y matrix contains averaged BOLD response in the four ROIs for the same participant. b) leave-one-out iteration of the PLS analysis. At every iteration data from one participant is excluded from the PLS analysis and later projected on the saliences obtained from the remaining (N-1) participants.
In PLS analysis the relationship between columns of $X$ and $Y$ is calculated by the cross product of the two matrices:

$$R = Y^T X \quad (4.1)$$

When $X$ and $Y$ are both centered (i.e., subtract column means), $R$ is the cross-covariance of the two matrices. The general problem of PLS is to find a new orthogonal basis that maximizes the covariance of linear projections of the original variables $X$ and $Y$. Among multiple solution algorithms that have been developed, the common approach in neuroimaging literature is to perform singular value decomposition (SVD) of the $R$ matrix following centering

$$R = U \Delta V^T \quad (4.2)$$

$$L_x = XV, L_y = YU \quad (4.3)$$

Where $U$ and $V$ are singular vectors of the $R$ matrix and will be referred to as saliences or components throughout this paper synonymously. $L_x$ and $L_y$ are called latent variables, which are the projection of the $X$ and $Y$ matrices on the right and left singular vectors, respectively. The SVD in PLS produces pairs of latent vectors $l_{x,i}$ and $l_{y,i}$ with maximal covariance and the additional constraints such that:

$$l_{x,i}^T l_{y,j} = 0 \text{ for } i \neq j \quad (4.4)$$

$$u_i^T u_i = v_i^T v_i = 1 \quad (4.5)$$
Where \( u_i \) and \( v_i \) are singular vectors of \( \mathbf{R} \). It follows from the properties of the SVD that the covariance of the pair of latent vectors \( l_{x,i} \) and \( l_{y,i} \) is equal to the corresponding singular value \( \delta_i \).

\[
l_{x,i}^T l_{y,i} = \delta_i \tag{4.6}
\]

While the SVD solution is suited to deal with high dimensional neuroimaging data, it corresponds to a fixed effect model and lacks generalizability, i.e., the discovered patterns are unique to the given dataset and do not necessarily reflect the population. Consequently, empirical approaches such as permutation tests are commonly used to identify significant and potentially generalizable latent vectors. In permutation testing, a null distribution is created by randomly permuting the order of observations for one set of variables (e.g., the \( \mathbf{X} \) matrix) and leaving the other set (the \( \mathbf{Y} \) matrix) unchanged. Repeating the permutation process and recalculating the PLS model for every iteration creates a distribution for the singular values under the null hypothesis. Therefore, saliences larger than an arbitrary \( p \) value (usually \( p<0.05 \)) are considered generalizable and retained for further analysis (Nichols, Holmes 2002).

While the permutation test is computationally efficient and provides simple and interpretable statistics, recent publications have demonstrated that it can be highly sensitive to outliers and result in biased parameter estimates (Kovacevic et al. 2013, Churchill et al. 2013). In cases where the overall effect size is weak simulation results by Kovacevic et al., demonstrate that this method is prone to high false positive rates. Moreover, their results suggest that the magnitude of singular values is not a reliable measure of the stability of the relationship between the patterns expressed by the saliences (Kovacevic et al. 2013). I propose a solution for the abovementioned problems by integrating the PLS analysis with bootstrapping of latent variables into a leave-one-out cross validation framework, which will be referred to as PLS-CV. This approach allows running the PLS analysis in a predictive fashion, which directly estimates the generalizability of the results (see (Gabrieli, Ghosh & Whitfield-Gabrieli 2015)).

The next step involves evaluating the stability of the variable patterns in each salience through resampling. To this end, a bootstrap resampling (i.e. resampling with replacement) is applied to the participant observations to estimate the standard errors of the saliences. For each element in a
salience, a bootstrap ratio is calculated by dividing its value by the standard deviation estimated from resampling. These bootstrap ratios are analogous to Z-scores and thus in neuroimaging applications elements with values larger than 2 (corresponding to p<0.05) are conventionally considered to show preliminary evidence of a significant, stable response. Note that standard multiple comparison considerations do not apply to such salience values as by construction they are strongly correlated variables within an SVD component.

An overview of the PLS-CV method is illustrated in Figure 4.1. In every iteration, one participant’s observations are set as the independent test sample \((X^o, Y^o)\) and the remaining data points are regarded as the training set. Data in the training set is mean centered and the same mean value (calculated on N-1 data points) is subtracted from the left-out observation prior to projection onto the training set saliencies. This ensures that all the model parameters calculated from the training set are applied to the test sample. Next, PLS analysis is run on the training set data and the test sample is projected onto the resulting bootstrapped saliences to obtain latent variables corresponding to the test data. Repeating this procedure for all samples in the dataset results in N sets of latent vectors, which are then averaged to generate the overall saliences of the cross-validated latent vectors.

\[
I^o_{x,i} = X^o V_i , I^o_{y,i} = Y^o U_i
\]  
(4.7)

\[
V = \frac{1}{N} \sum_i V_i , U = \frac{1}{N} \sum_i U_i
\]  
(4.8)

To measure the stability of the saliences across all N cross-validated training sets’ results, penetration maps were created by applying an absolute threshold value of 2 to the bootstrap ratio of saliences calculated at each iteration. The binarized, thresholded maps were then added together to represent the total number of cross validation sets of (N-1) participants that surpassed the threshold at every electrode channel. The results of this analysis are shown Figure 4.5a and Figure 4.7a. These plots illustrate the consistency of the salience patterns expressed across leave-one-out iterations. The stability of the fMRI saliences can be inferred from Figure 4.5b and Figure 4.7b where the bootstrap ratios across leave-one-out iterations and ROIs are depicted by boxplots.
Due to sensitivity of the PLS analysis to outliers, the EEG and fMRI data matrices were inspected before running the analysis and values that exceeded 2.5 standard deviations across participants were excluded from the analysis. Data from one participant was removed due to negative BOLD activity in three of the four visual area ROIs. Figure 4.2 and Figure 4.3 illustrate the distribution of the values in the EEG and fMRI data matrices and the outlier values removed from the analysis. As a result, data from three participants were removed.

Figure 4.2: Visual outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.
4.3 Results

The number of saliences in the PLS (and consequently PLS-CV) analysis is determined by the minimum number of variables in the X and Y matrices. In this case the Y (fMRI data) matrix included four variables representing four ROIs, hence the PLS-CV analysis yields four pairs of saliences and their corresponding latent variables. The PLS-CV results for the visual and auditory responses are provided in Figure 4.4 and Figure 4.6, respectively. Each row contains the plots associated with one pair of the PLS-CV saliences. These vectors will be referred to as EEG-CV (the EEG salience) and fMRI-CV (the fMRI latent salience). The percentage variance explained by each salience is included in the left side labels on the plot. The four iso-contour maps displayed in each row comprise one EEG-CV salience and represent the averaged bootstrap ratio for EEG salience, across all (N) leave-one-out cross validation iterations. The

Figure 4.3: Auditory outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.
contour lines on the iso-contour maps represent two levels of bootstrap ratio thresholds for statistical inference. The outer contour represents a bootstrap ratio of >2 (p<0.05 for Gaussian uncorrected distributions) and the inner contour represents a bootstrap ratio of > 2.6 (p<0.001 for Gaussian uncorrected distributions). The far right column shows the averaged bootstrap ratios for fMRI-CV saliences across the N training sets for each of the four ROIs. The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables (or scores). Each point on the plot corresponds to one participant and the black lines represent 95% confidence intervals for a linear regression fit.

The first visual EEG topographic map accounts for 57% of the joint covariance and shows significant occipital alpha ERD activity and left frontal alpha ERS, which are negatively correlated with the fMRI salience in the visual V1 ROI. Higher ERD values can be interpreted as higher pre-stimulus alpha power, which has been shown in previous literature to have a negative correlation with the visual BOLD response (Becker et al. 2011, Mayhew et al. 2013). The second and forth topographic maps do not show a stable correlation between EEG and fMRI latent variables. However, the third topographic map accounts for 15% of the joint covariance and shows positive occipital theta desynchronization, which shows a trend to being positively related to the fMRI response in V2 and has an opposite effect in V3. These results are supported by the stability maps illustrated in Figure 4.5, which show the consistency of both EEG and fMRI saliences patterns across leave-one-out iterations in components one and three. The penetration topographic maps in Figure 4.5a represent the number of participants that express an above threshold (bootstrap ratio >2) value at specific electrode channel and frequency band. The results suggest that the patterns captured by saliences are stable across the groups and that the primary spatial patterns seen in one and three are expressed in all of the participants’ results.
Figure 4.4: PLS-CV results for the visual response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographic maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of $p<0.05$ (*), or $p<0.001$ (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.
Figure 4.5: Stability of the EEG and fMRI saliences for the visual response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.
Figure 4.6: PLS-CV results for the auditory response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of p<0.05 (*), or p<0.001 (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.
Figure 4.7: Stability of the EEG and fMRI saliences for the auditory response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.
In the auditory domain, the first EEG topographic map accounts for 89% of the joint covariance and demonstrates strong theta ERS in the occipito-parietal area. The corresponding fMRI salience also shows strong response amplitude in all auditory ROIs except planum polare (i.e. A2, see Figure 3.2). The latent variables for EEG and fMRI saliences show a positive correlation. The second topographic map accounts for 6% of the joint covariance and shows a strong central theta and weaker central alpha ERD with a trend to a negative correlation to fMRI salience in the primary auditory cortex (A1) and an opposite effect in the planum tempolare (A3). In contrast to the first auditory and visual topographic maps this component seems driven by three participants who showed reduced alpha ERD (EEG scores of < -0.25) with strongly positive or negative BOLD responses in A1 and A3 (i.e. |fMRI score| > 0.3). The third and forth topographic maps do not show a stable correlation between EEG and fMRI latent variables. The stability results for the auditory components are provided in Figure 4.7. Similar to the visual results, the prominent auditory components show consistency in both EEG and fMRI saliences.

4.4 Discussion

In this work I proposed a multivariate analysis framework to study the effect of task-related changes in the brain oscillatory activity (ERD/ERS) and their relationship to the evoked BOLD response in auditory and visual domains.

4.4.1 Visual results

The first component of the visual results comprises 57% of the total covariance and includes activity in the alpha band. While no previous studies has directly investigated the relationship between ERD/ERS and the BOLD signal, high values of ERDs can be interpreted as higher pre-stimulus power in the frequency band involved. Therefore, in Figure 4.4 the negative correlation in component one between occipital alpha ERD and the V1 ROI conforms with previously reported results (Mayhew et al. 2013). It should be noted that this finding does not necessarily conflict with those of Becker et al., which show a correlation between alpha activity and the evoked BOLD response outside of the V1 area (Becker et al. 2011). As discussed earlier, the implications of alpha rhythm on the BOLD response could depend on the brain state and the vigilance level (Olbrich et al. 2009, Wong et al. 2013, Wong, DeYoung & Liu 2016, Wu, Eichele & Calhoun 2010). For instance, in a study by Wong et al., the relationship between
different EEG frequency bands (e.g. delta, theta and alpha) and the BOLD signal was found to be different during eyes-open versus eyes-closed acquisition (Wong et al. 2013). The results from Becker et al., report changes in the alpha power during a visual oddball task, which could reflect different states of vigilance and neural processing compared to results from our passive experiment. The third component however, reveals a subtle yet stable association between occipital ERD in the theta band and the BOLD response in V2 and V3. The increase of posterior theta activity has been linked to drowsiness and decreased alertness (Tsuno et al. 2002). Thus differences in participant state related to alertness, vigilance and drowsiness as differentially reflected across the frequency bands may be significant modulators of experimental results attempting to relate BOLD fMRI and EEG signals.

4.4.2 Auditory results

The auditory results demonstrate a prominent occipital theta ERS in the first component, which shows a stable correlation and significant relationship to auditory ROIs except in the planum polare. The significant ERS in the theta band can be attributed to the slow wave auditory P3, which is a slow wave time-locked to the auditory stimuli with most of its energy concentrated in the theta band. The spatial distribution of theta power in this PLS-CV component matches that of the auditory P3wave (Picton 1992).

The second auditory component consists of central alpha band ERD as well as frontocentral theta ERD, which shows negative correlation with fMRI values in the primary auditory cortex and planum temporale. The existence of auditory alpha rhythm and auditory ERD in the alpha band has been demonstrated in previous studies (Krause et al. 1994, Krause 2006). The extracted alpha ERD in the second component shows similar topographical distribution of the auditory evoked response and matches the spatial distribution for alpha ERD reported in previous studies.

With the exception of the first component, the auditory components show smaller effects (corresponding to smaller variance percentage) compared to the visual components. These could be due to the fact that oscillatory activity of the auditory cortex is less obvious and often masked by the particularly prominent occipital and sensory motor rhythms (Weisz et al. 2011). The small spatial extent of the auditory cortex and the large extent of anatomical variations in its
orientation across participants makes precise measurement of pure cortical auditory oscillations a challenging task.

### 4.4.3 Potential extensions and applications of the proposed model

The present study illustrates how a multivariate framework can be used to investigate the relationship of broadband EEG oscillations and the fMRI BOLD signal. The common approach for integrating simultaneous (or separately recorded) EEG oscillations and fMRI data is to extract specific frequency band powers from EEG data and incorporate them as regressors in a GLM model to determine brain regions whose BOLD responses covary with changes in oscillatory power. A disadvantage of the GLM as a univariate model is that it does not account for network interactions in the brain. These interactions are manifested both in EEG and fMRI data. These results combined with recent literature suggest that study of single band EEG oscillations provides an incomplete picture of the neural dynamics of the brain and accounts for some of the discrepancies reported in the literature (Mantini et al. 2007, Laufs et al. 2006, Olbrich et al. 2009, Wong et al. 2013, Wong, DeYoung & Liu 2016). Interaction between different frequency bands becomes even more critical in the study of sophisticated cognitive tasks as the same regions of the cortex can demonstrate different spectral profiles depending on the cognitive process that they are involved in (Donner, Siegel 2011).

In this study the fMRI response was evaluated in ROIs. While this process can improve SNR of the BOLD response and enables focusing on the sensory response, the proposed method can be readily extended to perform whole brain analysis to study global signal and cognitive responses beyond sensory cortices.
Chapter 5: Task-Related BOLD Signal and EEG Oscillations in the Sensory Cortices

5.1 Introduction

Spontaneous fluctuations are a ubiquitous feature of brain signals that have been captured by different imaging modalities and across a wide range of experimental paradigms. While these variations were traditionally perceived as noise, evidence from both EEG and fMRI studies suggest that these fluctuations reflect underlying neural mechanisms and can contain important information, even more so than the mean BOLD response, about the brain functionality (Garrett et al. 2010, McIntosh et al. 2010, McIntosh, Kovacevic & Itier 2008). Variability in the brain’s response is not limited to the BOLD signal. It has been established across species and modalities. Invasive animal studies have revealed neural sources for variability in the electrophysiological response as well (Arieli et al. 1996). However, since fMRI provides indirect measures of neuronal activity, it is unclear how BOLD signal variability relates to other measures of spontaneous neuronal activity.

Simultaneous EEG-fMRI provides a suitable platform to probe the relationship between variations in the BOLD signal and spontaneous neural activity. Several simultaneous EEG-fMRI studies have demonstrated links between neural oscillations and BOLD response fluctuations (Laufs et al. 2003b, Laufs et al. 2003a, Becker et al. 2011, Scheeringa et al. 2011, Mayhew et al. 2013, Wu, Eichele & Calhoun 2010, Fox et al. 2006). For instance, a relationship between occipital alpha band power and variability of evoked BOLD response was reported in sub-regions of the visual cortex (Becker et al. 2011, Mayhew et al. 2013). Similarly, task-induced BOLD response and desynchronization in the rolandic alpha and beta bands were found to co-localize in the somatosensory and motor cortices (Yuan et al. 2010). While all of the above mentioned studies provide evidence for the existence of neural sources for BOLD signal fluctuations, there is a lack of consensus regarding the type and the location of the relationship
between neural oscillations and the BOLD response. For instance, Becker et al., observed a negative linear correlation between the pre-stimulus alpha power and the visual BOLD response in extrastriate areas (Becker et al. 2011). In contrast, Mayhew et al., reported negative correlation between pre-stimulus alpha power and the visual BOLD response in the primary visual cortex (V1), and parts of the LGN for higher contrast visual stimuli (Mayhew et al. 2013). Scheeringa et al., found no significant relationship between pre-stimulus alpha power and fMRI visual response, but instead observed a correspondence between the phase of the alpha rhythm at the stimulus onset and the visual BOLD response (Scheeringa et al. 2011). Studies that investigated task-induced synchronization/desynchronization of the oscillatory activity have reported spatial correlation with the BOLD response but no consistent correlation in the magnitude of the response across participants (Winterer et al. 2007).

In resting state studies, different patterns of correlation between alpha band power and BOLD signal fluctuations have been reported (Laufs et al. 2006, Goncalves et al. 2006). While within participant results show more consistency, correlation patterns across the participants are shown to vary in sign and location. Furthermore, including additional frequency bands (e.g. theta and beta) in the analysis is shown to be helpful in explaining some of the inconsistencies in the results (Mantini et al. 2007, Laufs et al. 2006), and reveals relationships between resting fMRI networks and EEG frequency bands (Mantini et al. 2007, Lei et al. 2014). There is also evidence that fluctuations of fMRI and EEG signals may partly reflect a small number of quasi-stable microstates, which are not closely linked to the traditional EEG frequency bands (Britz, Van De Ville & Michel 2010).

It has been suggested that the correspondence between neural oscillations and the BOLD signal dependents on the brain state and the task being performed (e.g. cognitive task, eyes-open rest, eyes-closed rest etc.) (Wong, DeYoung & Liu 2016, Wu, Eichele & Calhoun 2010). Furthermore, while performing the same task, the relationship between BOLD and oscillations depends on the participants’ level of vigilance and alertness (Laufs et al. 2006, Goncalves et al. 2006, Olbrich et al. 2009, Wong et al. 2013). Despite several attempts to quantitatively measure vigilance using oscillatory power in different frequency bands of the EEG data, the role of vigilance in the EEG-BOLD coupling remains unclear. This is in part due to the lack of a coherent definition of “vigilance” in the literature. As it has been pointed out by Oken et al.,
“The field has been hindered by inconsistent or poorly defined terminology. Researchers should be particularly careful about the usage of the term vigilance (Oken, Salinsky & Elsas 2006).” The term vigilance has been used arbitrarily in sleep, resting state and cognitive studies and depending on the particular experimental conditions of the study, different neurophysiological signatures have been reported.

Furthermore, many of the previous studies of EEG oscillatory activity have focused on spatially constrained activity in a single frequency band (e.g. the occipital alpha). However, the functional significance of different frequency bands can vary depending on the measurement site, process and cognitive state (Donner, Siegel 2011, Olbrich et al. 2009, Lei et al. 2014, Cantero et al. 2003).

The goal of this chapter is to characterize the relationship between EEG measures of spontaneous neural oscillations, which may reflect vigilance and/or alertness, and task-related BOLD responses. This is accomplished by applying the multivariate framework described in Chapter 4. In particular, I will examine the data-driven, multivariate relationship between multiple frequency bands from all EEG channels and the task-dependent fMRI signal from ROIs in the visual and auditory cortices in response to the passive audiovisual stimulus task. Due to its ability to handle high dimensional data, the proposed method enables simultaneous analysis of EEG data across multiple frequency bands and channels. This provides an advantage over conventional approaches where the analysis of EEG oscillations is limited to a certain frequency band or few electrode channels. Furthermore, the multivariate approach allows extraction of relationships across multiple ROIs. Hence it provides a more comprehensive image of the underlying oscillatory and BOLD signal dynamics that are generated by the stimulus compared to the conventional methods.

5.2 Methods

Data was collected by administering the audiovisual paradigm described in Chapter 2. The results provided in this chapter are based on analysis from participants from all three phases of
the recruitment (N = 20). Data from two subjects were removed from further analysis due to excessive head motion (max. displacement > 3mm, see Chapter 3 for details).

The fMRI pipeline and the EEG processing pipeline applied in this Chapter are the same as those in Chapter 4. The average β values calculated in visual and auditory ROIs will be used as the fMRI features in this chapter. The EEG processing steps included MR and BCG artifact correction, bandpass filtering, bad channel detection, ICA artifact removal, bad channel interpolation (see Chapters 2 & 3 for more details on each processing step). These steps were followed by spectral analysis of the EEG data. After applying a short time Fourier transform to the EEG data (see Chapter 4 for details), the relative frequency band power at every time point was calculated as the ratio of the average power within the band to total signal power (i.e. across all frequency bands). Then, for each channel and frequency band, the median of the relative band power was calculated across all time points and used as the EEG feature in the PLS-CV analysis.

Similar to the previous Chapter, the EEG (and fMRI) data matrix was mean centred in this analysis and left and right sided responses were averaged together to increase the SNR. Similarly, each row of the fMRI data matrix included BOLD responses in four ROIs, averaged for left and right-sided stimuli.

Due to sensitivity of the PLS analysis to outliers, the EEG and fMRI data matrices were inspected before running the analysis and values that exceeded 2.5 standard deviations were excluded from the analysis. Furthermore, data from one subject was removed due to negative BOLD values in the majority of the visual areas. Figure 5.1 and Figure 5.2 illustrate the distribution of the values in the EEG and fMRI data matrices and the outlier values removed from the analysis. As a result, data from three participants were removed from visual and auditory data matrices (N=15).

There is some evidence in the literature suggesting that motion induced artifacts in the EEG oscillatory measures may produce plausible correlations with the BOLD response (Jansen et al. 2012). Since the EEG measures used in this chapter are not time-locked to the stimuli (in contrast to Chapter 4), additional analysis was performed to examine the possible contribution of confound motion artifacts to the PLS-CV analysis results. The PLS-CV analysis was performed by substituting the BOLD values with the six motion parameters for each participant. The motion
parameters were derived from the rigid motion correction step in the fMRI preprocessing (see Chapter 3) and included motion estimates in roll, pitch, yaw, superior (dS), left (dL) and posterior (dP) directions. The PLS-CV topographic maps associated with EEG saliences from this analysis were then compared to those obtained from PLS-CV analysis on the EEG oscillatory measures using the Jaccard similarity coefficient. The Jaccard coefficient calculates the similarity between two sample sets, A and B, and is defined as the ratio of the size of intersection between the samples to the size of their union:

\[ J(A, B) = \frac{|A \cap B|}{|A \cup B|} \]  \hspace{1cm} (5.1)

The stable variables within each component were identified by applying a binary threshold of > |2| to the bootstrap ratios of EEG saliences. Then a pair-wise comparison of the thresholded saliences was performed using Jaccard similarity coefficient:

\[ J_{p,q} = \frac{\sum_{k=1}^{N} C_{p,k}C_{q,k}}{N} \]  \hspace{1cm} (5.2)

Where \( J_{p,q} \) is the Jaccard similarity coefficient between component p (from the motion PLS-CV analysis) and component q (from EEG oscillatory PLS-CV analysis). \( C_p \) and \( C_q \) are binary thresholded EEG saliences from the PLS-CV analysis using motion parameters and EEG oscillatory measures respectively. And N is the number of variables (i.e. 252) in each component.
Figure 5.1: Visual outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.
Figure 5.2: Auditory outliers. The left panel illustrates the BOLD response values in four ROIs for all participants. The right panel shows the average band power in four frequency bands for all participants. The dashed red line represents three standard deviations. The red circles indicate outlying values belonging to participants that were removed from the analysis.
5.3 Results

The PLS-CV results for the visual and auditory responses are provided in Figure 5.3 and Figure 5.4 respectively. Each row contains the plots associated with one of the PLS-CV saliences, hereafter referred to as EEG-CV (EEG saliences) and fMIR-CV (fMRI saliences). The percentage variance explained by each latent vector is included in the left side labels on the plot. The iso-contour maps displayed in each row represent the EEG saliences as bootstrap ratios visualized in the four frequency bands. The contour lines on the iso-contour maps represent two levels of bootstrap ratio thresholds for statistical inference. The outer contour represents a bootstrap ratio of $>2$ ($p<0.05$ for uncorrected Gaussian distributions) and the inner contour represents a bootstrap ratio of $>2.6$ ($p<0.001$ for uncorrected Gaussian distributions). Note that because these are latent vectors from a covariance decomposition the usual requirement for multiple comparison corrections under an assumption of uncorrelated voxels doesn’t apply because all iso-contour map saliences are correlated by construction. The far right column shows the bootstrap ratios for fMRI saliences across four ROIs. The scatterplots in the second to right column show the correlation between cross-validated EEG and fMRI latent variables. Each point on the plot corresponds to one participant and the black lines represent 95% confidence intervals.

The stability results for visual and auditory components are provided in Figure 5.4 Figure 5.6 respectively. The penetration topographic maps represent the number of participants that express an above threshold (bootstrap ratio $>2$) value at specific electrode channel and frequency band. The results suggest that the patterns captured by saliences are stable across the groups and are expressed at least in more than half of the participants’ results.

Figure 5.3 illustrates the analysis results for the visual response. The first visual component accounts for 58% of the joint covariance and shows a marginally significant relationship between the EEG and BOLD saliences. The EEG topographic maps associated with the first component show a bilateral negative and central positive change in activity in the theta band. The positive central theta activity shows higher significance in the frontal and occipital regions. The alpha band shows subtle positive right frontal activity. In the beta frequency range, a negative central and positive bilateral temporal pattern is observed in the beta1 band. The beta2 band shows a
weaker centro-parietal positive pattern. These spatial distributions are negatively correlated to the BOLD signal variance in visual ROIs with the strongest, and only significant relationship observed in the visual area V1.

Figure 5.3: PLS-CV results for the visual response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of p<0.5 (*), or p<0.001 (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.
Figure 5.4: Stability of the EEG and fMRI saliences for the visual response. a) Penetration maps for the EEG visual components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.
The second and third saliences do not show a stable correlation between EEG and fMRI latent variables. But the EEG saliences in component 4 (7% of the covariance) explain the variance patterns associated with the BOLD activity in V4 (area MT) through a negative correlation with significant focal saliencies distributed across all bands.

Results for the auditory modality are presented in Figure 5.5. The first component contains 58% of the covariance and shows a negative correlation between EEG and fMRI saliences. EEG saliences for component 1 reveal a positive occipital theta band pattern, negative occipital alpha and bilateral positive fronto-temporal alpha and beta band activity. These patterns are negatively correlated with the changes in the BOLD signal in A3 (planum tempolare) and A4 (lateral superior temporal gyrus). The remaining components, 2 to 4, show significant EEG saliences in various frequency bands without any significant relationship to the fMRI ROI saliences. In fact the fMRI versus EEG plots per participant seem primarily driven by a few fMRI outliers with relatively weak ROI signals compared to those in component one. These results are supported by the stability maps illustrated in Figure 5.6, which show the consistency of both EEG and fMRI saliences patterns across leave-one-out iterations.
Figure 5.5: PLS-CV results for the auditory response. Each row contains plots corresponding to one component. The values on the left indicate the percent variance explained by each component. The four topographic maps in each row illustrated the EEG salience vector, which consists of four frequency bands. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding fMRI salience vector in the four ROIs. The asterisk indicates a significance level of $p<0.5$ (*), or $p<0.001$ (**). The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.
Figure 5.6: Stability of the EEG and fMRI saliences for the auditory response. a) Penetration maps for the EEG auditory components. The heatmaps indicate the number of participants whose saliences surpass the threshold value of 2 at every electrode channel. b) Distribution of fMRI saliences for across leave-one-out iterations for each of the ROIs. The black line in the centre of the box plot represents the median.
Figure 5.7: PLS-CV results using fMRI motion parameter estimates (roll, pitch, yaw, dS, dL, dP) instead of the BOLD response. Each row represents results with one pair of components and latent variables. The topographic maps on left show the spatial distributions of the EEG oscillatory power that may confounded with motion related BOLD signal. All topographical maps are plotted with the same color scale, as shown in the bottom left corner, and illustrate bootstrap ratios for the EEG salience vectors. The far right column represents bootstrap ratios for the corresponding motion fMRI salience vectors. The scatterplots in the second to right column show the correlation between EEG and fMRI latent variables.
Results from the motion PLS analysis are provided in Figure 5.7. Performing the PLS analysis using the six motion parameters results in six components (illustrated in Figure 5.7). The first component comprises 38% of the variance with EEG topographic saliences showing mostly frontal theta and bilateral parietal alpha activity. These patterns show the strongest trend associated with motion parameter estimates in pitch, dS and dP directions. The Jaccard similarity coefficients calculated for each of these six components and the four components from the original PLS analyses were found to be in the range of [0, 0.03] for the visual components and [0, 0.04] for the auditory components.

### 5.4 Discussion

In this chapter I aimed to investigate the relationship between variability in the amplitude of the sensory BOLD responses and participants’ alertness/vigilance state as reflected in their ongoing asynchronous EEG activity. I hypothesized that mental signatures of the brain’s vigilance state can be captured using spontaneous oscillatory activity of the brain in different frequency bands. To this aim, I used a multivariate analysis framework to study co-variations between the brain’s state, explained by broadband oscillatory activity in the EEG signal, and the BOLD response amplitude across participants.

Most of the previous studies that have addressed the links between brain oscillations and the BOLD response have limited their measurement to one or two frequency bands recorded from a predetermined electrode site. The measured oscillatory powers are then typically incorporated in a univariate GLM analysis to extract brain regions whose BOLD signal co-vary with the EEG oscillations. However, this approach does not provide a complete picture of the underlying oscillatory dynamics since oscillations of different frequencies can coexist and interact with each other, resulting in a wide range of brain states (Daunizeau, Laufs & Friston 2009). Moreover, this approach relies on assumptions regarding participant’s vigilance/cognitive state to select the relevant frequency band and electrode site.

There are also methodological limitations imposed by the univariate model. The loss of statistical power prohibits including a large number of predictors (i.e. multiple frequency bands and
channels) in the model and the univariate framework is inherently incapable of extracting interaction between different frequency bands.

The efficiency of PLS techniques in dealing with high dimensional data, makes it feasible to include multiple frequency bands and electrode sites simultaneously in the analysis, and thus eliminate the need to make any assumptions about the brain state. The added cross validation step helps to deal with potential false positive results reported by PLS and improves the likely generalizability of the results.

For both visual and auditory analyses, the first component contains the highest percentage of variance explained and demonstrates a significant coherent relationship between EEG and fMRI. The first visual component shows a negative relationship between the variations in the amplitude of the BOLD response in the visual area V1 and the EEG saliences. The first frequency band topographic map shows a prominent positive central theta activity, which is most strongly manifested in the occipital area. The increased occipital theta power has been associated with decreased levels of alertness (Olbrich et al. 2009). Also, previous studies of spontaneous theta activity suggest that increased prestimulus theta level can result in a decrease in the amplitude of the visual EPs (Rahn, Basar 1993, Basar et al. 1997).

The first component in the auditory analysis also demonstrates negative correlation between the EEG salience and the BOLD signal in the planum temporal and lateral superior temporal gyrus. The auditory topographic maps show an increase in the occipital theta power, decrease in the occipital alpha and increase in the frontal alpha power, decreased central and increased temporal beta1 band power. The increase in occipital theta power in the first auditory and visual EEG saliences and the fact that they both conform to the previously reported EEG signatures of vigilance and their negative correlation with the BOLD response could suggest that these EEG saliences represent a frequency band signature that describes a general reduction in alertness and affects the sensory response in participants.

Both modalities have strong results for higher order sensory areas: planum temporale and lateral superior temporal gyrus in the first auditory component, and area MT for the fourth visual component. The implications of the lateral auditory areas in higher order attention related response modulations has been shown with high resolution fMRI imaging of the auditory cortex.
The forth visual component comprises small percentage (7%) of the total variance, but demonstrates a stable relationship in the area MT. While there is evidence of implication of area MT in spatial attention (Womelsdorf et al. 2006, Beauchamp, Cox & DeYoe 1997), there is not much literature directly bearing on the role of area MT and the associated oscillatory patterns (represented in the fourth component) in the sensory processing. The relationship in component four can further be explored in the future by studying the left and right sided responses separately.

To examine the possible influence of head motion on driving correlation between EEG and fMRI saliences (Jansen et al. 2012), PLS-CV analysis was repeated with bold values replaced with motion parameter estimates. The most prominent patterns in the topographical maps resulting from the PLS-CV motion analysis include frontal theta and centroprietal alpha activity in the first component, and occipitoparietal theta activity in the second component. While there is very limited evidence on the correlation between different EEG frequency bands and head motion in EEG-fMRI, the frontcentral theta pattern in the first component conforms with the results reported in literature (Jansen et al. 2012). It should be noted that even the first component does not achieve a stable correlation between the latent variables. The comparison of motion related topographic maps shown in Figure 5.7 and those from original PLS-CV analyses (shown in Figure 5.3 and Figure 5.5) demonstrated minimal overlap between motion driven and response driven components.

Another important consideration while interpreting the results from joint fMRI and EEG analysis is the impact of EEG processing parameters on the results. It has been shown that the choice of processing parameters, type of power band value (i.e. relative versus absolute power band value) may have a direct impact on detecting BOLD correlates of EEG frequency bands (Labounek et al. 2015). While the best choice of EEG frequency band measure for EEG-fMRI analysis is an understudied topic, current findings suggest that relative EEG frequency band power, as used in this chapter, may have advantages in capturing neural correlates in BOLD signal variability (Jansen et al. 2012). Additionally, since abrupt head movement tends to create broad-spectral EEG spikes, relative EEG band power comprises a measure that is more robust to head movement artifacts.
EEG-fMRI is the combination of two prevalent neuroimaging techniques, EEG and fMRI, which enables simultaneous study of brain functionality with the spatial resolution of fMRI and temporal resolution of EEG. Moreover, the two imaging modalities are complementary in the sense that one represents the underlying electrophysiological response and the other reflects the hemodynamic physiological response of the brain. Since its introduction to the field of neuroimaging in the last decade, the application of EEG-fMRI in various areas of clinical and cognitive neuroscience has grown exponentially. In clinical neuroscience, EEG-fMRI has been applied to study spontaneous brain activity such as ictal and interictal epileptogenic discharges as well as brain oscillations during sleep. Another popular area of application for EEG-fMRI has been localization of ERP components that have long been studied in cognitive and sensory EEG paradigms. Moreover, concurrent recording of the EEG and BOLD response has improved our understanding of neurovascular coupling and the relationship between the neural and physiological response.

Despite all the potential benefits and applications, EEG-fMRI poses unique challenges. The most important challenge is the compromise to EEG data quality. The EEG data recorded inside the scanner is contaminated by MR gradient and ballistocardiogram (BCG) artifacts. Over the last decade, multiple approaches have been proposed to remove these artifacts from EEG data. Although advances in artifact removal techniques have made it possible to obtain EEG data with acceptable quality in the MR scanner, efficient removal of BCG artifact still poses a challenge.

In Chapter 2, I presented an evaluation and comparison of the mainstream BCG artifact removal approaches as implemented in commercial and non-commercial software packages. The results from Chapter 2 demonstrated that the performance of the artifact removal method can significantly improve by taking into account BCG artifact variability across participants and experimental conditions and tuning the correction parameters accordingly. It was also shown that optimizing the correction parameters for individual dataset can improve the signal to noise
ratio (SNR) of the extracted event-related potentials (ERP) and achieve SNR levels comparable to recording conditions outside the scanner. The proposed method in Chapter 2 was used to analyze the EEG data and extract the auditory and visual ERP responses that were presented in Chapter 3.

While the proposed method in Chapter 2 significantly improves the SNR of ERPs, its application is limited to event-related studies. A potential area of improvement would be to develop an adaptive correction algorithm, where the correction parameters are estimated for each dataset. This topic has been the goal of an ongoing collaboration with the Department of Mathematics at the University of Toronto. Currently, a new correction method is being developed that allows for adaptive correction of the BCG artifact based on features extracted from each dataset. Because this method does not rely on the SNR measure from the ERPs, it can be applied to studies of spontaneous and ongoing brain activity (e.g. resting state studies).

The third chapter of this work investigated the relationship between the BOLD response and ERP components in the context of a sensory paradigm. The majority of the published results in the EEG-fMRI literature focus on the later cognitive ERP components, and presently there is no consensus on BOLD correlates of the sensory ERP components. As discussed in Chapter 3, these inconsistencies can be attributed to methodological shortcomings, differences in the experiment conditions as well as the neural feedback mechanisms that are involved in the generation of sensory ERP components (Muler 2010, Di Russo et al. 2002, Di Russo, Martinez & Hillyard 2003). Furthermore, most of these studies have applied asymmetrical integration approaches built on the assumption of complete overlap of the BOLD and EEG responses, which is not always the case. The mismatches in the extent of EEG and BOLD responses, can bias the results from asymmetrical integration approaches. In Chapter 3, an independent analysis of the EEG and fMRI data was performed and the relationship between the two modalities was investigated at two levels: within participants and between participants. The results showed a relationship between different ERP components and the BOLD response in the auditory and visual cortices at the between-participant level. However, no significant within-participant relationship was observed. When the BOLD response in the sensory cortices was divided into specific sub-regions, the relationship for some of the ERP components improved, while for other components the relationship deteriorated. This observation can be explained by the fact that ERP components
have generators in several regions of the sensory cortices and each cortical patch may contribute
to the generation of more than one ERP component. Extending this idea suggests that the nature
of the relationship between the ERP components and the BOLD signal is not a unique one-to-one
relationship. This scenario makes a univariate approach an unsuitable analysis choice because it
cannot model the interaction between multiple patches or other variables.

Thus, a multivariate analysis was adopted in Chapters 4 and 5 to study the EEG-BOLD
relationship. Another possible source of inconsistency in the ERP-BOLD results, also addressed
in Chapter 4, was that the traditional ERP analysis only captures the phase-locked response in the
EEG data. However, the phase-locked response represented by the ERPs constitutes only a part
of the brain’s evoked response. There is growing support in the literature that the time-locked
neural response may be a preferred choice in studies of the EEG-BOLD relationship (Siegel,
Donner 2010, Donner, Siegel 2011). Hence, in Chapter 4 a broad-band spectral representation of
time-locked EEG evoked responses was used to study the event-related BOLD-EEG relationship.

Unlike univariate approaches, multivariate techniques can explore the full spectrum of available
information in EEG-fMRI data. The multivariate technique used in Chapter 4 to analyze ERP-
BOLD relationship was based on partial least square (PLS). PLS is multivariate technique that
aims to maximize the covariance between two sets of variables by finding new orthogonal bases.
Although the technique has been successfully applied in the field of neuroimaging (McIntosh,
Lobaugh 2004, Krishnan et al. 2011, McIntosh et al. 1996), recent results suggest that it can be
prone to false positives and overfitting (Kovacevic et al. 2013, Churchill et al. 2013). To address
this problem, in Chapter 4, PLS was implemented in a leave-one-out cross validation framework
(PLS-CV), where the estimated components and projections were calculated through an iterative
procedure. Incorporating PLS in such a framework increases the generalizability and reliability
of the results. Furthermore, this analysis does not suffer from limitations of the asymmetrical
approaches.

The described method was applied to measures of event-related synchronization (ERS) and
event-related desynchronization (ERD) from the EEG data and the BOLD response across
different ROIs in visual or auditory cortices. The ERD/ERS were calculated as changes in the
EEG oscillatory power across different frequency bands at every electrode channel. The analysis was the first of its kind, providing results that were consistent with the previous literature.

In addition, comparison of primary subregions between results in Chapters 3 and 4, helps to explain the complex interactions between multiple cortical patches and their role in associations between BOLD fMRI and EEG signals. Results from Chapter 3, Table 3.1 for visual stimuli show the strongest fMRI-ERP associations between V2 for the early P1 and N1 ERP components and V4 with N1. In contrast in Chapter 4 the strongest associations are between V1 and a complex alpha band response involving unilateral frontal and posterior regions, and more weakly between V2 and V3 and a bilateral strongly posterior theta response. Thus all four sub-regions are implicated in BOLD fMRI associations with phase-locked early ERP amplitudes or time locked frequency bands during the stimulus window. These results clearly show a broad range of fMRI-EEG relationships, which are strongly dependent on the exact analysis methodology used even given the same stimulus response data.

Results from Chapter 3, Table 3.2 for auditory stimuli show noisier fMRI-ERP associations between single ERP peak results for P2 and N1 across A1-A3. These only appear as strong as the visual relationships when testing N1-P2 across A1 and A3, with A2, while significant having a much lower association slope. In contrast, in Chapter 4 there is a very large association between A1, A3 and A4, and a bilateral posterior theta response, which is probably related to auditory P3. While showing that the time-locked frequency band response may in fact reflect ERP features other than those tested in Chapter 2, we again see all four sub-regions significantly implicated in fMRI-EEG associations. Future work should test replication of these visual and auditory results and then use the PLS-CV technique to try to understand the relationship between the literature focusing on ERP peak structure, the time-locked frequency bands and regional BOLD fMRI associations.

The proposed PLS-CV method can also be used to study task related responses in more complex cognitive paradigms. The modulations of neural oscillations in working memory tasks have been demonstrated in previous studies (Meltzer et al. 2008, Brookes et al. 2011, Freunberger et al. 2011, Klimesch 2012, Roux, Uhlhaas 2014). However, the precise implication of each oscillatory band, their cortical sources and their relationship to the associated BOLD response
during working memory performance is not well understood. The PLS-CV method is currently being applied to a previously collected dataset at the Rotman Research Institute to study the brain mechanisms involved during a working memory task. The dataset contains simultaneously recorded EEG and fMRI data collected to investigate neural and BOLD correlates of proactive interference. Proactive interference is the ability to suppress irrelevant information that is stored temporarily in the working memory. The effect was produced by administering a variant of the Sternberg memory task (Sternberg 1966), called the recent probe paradigm. A block diagram of the trial structure and conditions in the paradigm is provided in Figure 6.1. In the encoding phase of each trial participants were presented with a small set of letters (1.5s). This was followed by a retention interval during which a fixation cross appeared on the screen (3s). Next, a probe letter was presented and participants were asked to respond whether the letter was included in the immediately preceding memory set (i.e. positive), or not (i.e. negative). Furthermore, depending on the presence of the probe in the previous trials, the probe can be labeled as recent or non-recent. This results in four probe conditions in total: Positive recent, positive non-recent, negative recent and negative non-recent.
The effect of proactive interference can be studied by contrasting the negative recent trials versus the negative non-recent trials. The negative recent trials are associated with lower response accuracy and higher reaction times. This decay in the performance is indicative of proactive interference (Jonides et al. 1998, Zhang et al. 2010).

The existing EEG-fMRI literature of the Sternberg task has focused on the retention period and BOLD correlates of neural oscillations during this period (Scheeringa et al. 2009, Michels et al. 2010, Meltzer et al. 2007). The PLS-CV method can be applied to perform a multi-band frequency analysis of the EEG-BOLD relationship during the retention period. Furthermore, no study so far has examined the relationship between the event-related changes in EEG oscillations
and fMRI response during the probe presentation, which sheds light on the mechanisms of proactive interference. The PLS-CV can be adopted to analyze ERD/ERS elicited by the proactive interference effect across multiple frequency bands and channels and their relationship to the BOLD response. A brief description of the working memory dataset as well as preliminary analysis results from the dataset is provided below.

A total number of 17 participants were recruited for the experiment (mean age = 24 years, SD = 4.0, 5 males). Data from 15 participants were included in the analysis, as there were technical problems and incomplete recording sessions for 2 participants. Initial analysis of the data revealed signatures of proactive interference in both EEG and fMRI data. Individual participant fMRI data analysis was performed using the fMRI pipeline described in Chapter 3. EEG data analysis was performed for individual participants based on the methods explained in Chapter 2, except that the ballistocardiogram artifact correction was performed using the default settings (i.e. correction with 3 principal components). The preliminary results provided in Figure 6.2 and Figure 6.3 illustrate the group analysis results for fMRI and EEG data respectively, which are characteristic of proactive interference.

Figure 6.2 : Group averaged ERP waveform indicating the proactive interference effect. The waveforms represent averaged ERPs recorded for the Negative Non-recent (in blue) versus Negative Recent (in red) stimulus condition. The waveforms are recorded at the Cz electrode and the difference in peak amplitude at ~200 ms and ~500ms represent proactive interference.
Figure 6.3: Group level fMRI SPMs for the proactive interference effect. The SPMs are t-values thresholded at $p<0.001$ with a cluster size of 40 voxels.
The ERP analysis results in Figure 6.2 illustrates the group averaged ERP waveform for the negative non-recent and negative recent conditions, recorded at the site of Cz electrode. The increased positivity at ~200ms and increased negativity at ~500ms for the negative recent condition represent the proactive interference effect (Zhang et al. 2010, Du et al. 2008). The fMRI results for the proactive inference (i.e. recent negative versus non-recent negative contrast) are shown in Figure 6.3. The results show increased activation in the left lateral prefrontal cortex (LPFC) area, which are shown to be associated with this effect (D'Esposito et al. 1999, Badre, Wagner 2005, Nee, Jonides & Berman 2007).

In Chapter 5, the PLS-CV method was adopted to study the relationship between spontaneous EEG oscillations and the task-induced BOLD evoked response in auditory and visual cortices. A number of studies have examined the effect of ongoing alpha band activity on the task-induced BOLD response. The results are variable depending on the experimental conditions and the corresponding cortical region. For instance, while results in the somatosensory cortex agree with the general inhibitory role of the alpha rhythm, the results in the visual cortex are less consistent. Reports from previous studies in the visual cortex range from no alpha-evoked BOLD relationship to a linear relationship (Becker et al. 2011, Scheeringa et al. 2011, Mayhew et al. 2013). As was pointed out in Chapter 5, a potential underlying cause of these inconsistencies is the limited scope of EEG analysis, which is usually confined to a single frequency band and electrode site. However, evidence suggests that the implications of each EEG frequency band on the BOLD signal should be considered in relationship to other frequency bands and the electrode site it is measured from. Furthermore, the functional role of frequency bands varies depending on the brain state (e.g. vigilance) (Laufs et al. 2006, Goncalves et al. 2006, Goncalves et al. 2006, Wong et al. 2013). This issue is further complicated by the lack of a coherent definition of vigilance in the literature (Oken, Salinsky & Elsas 2006). The proposed framework in Chapter 5 enabled the simultaneous presentation of multiple frequency bands in the analysis, without the need of making any pre-assumptions about the brain state and their functional relevance. I found clear evidence of relationships between different frequency bands of spontaneous EEG oscillations and regional fMRI task-linked signals. For example, Fig. 5.3 shows that the V1 fMRI response is modulated by ongoing EEG oscillations, which may partly explain the noisier associations seen in V1 compared with V2 and the P1 and N1 ERP peaks in Chapter 3. Using the
techniques developed in this thesis to tease apart the various fMRI-EEG associations for phase-locked and time-locked task responses in EEG is an important direction for future work.

In addition, a natural extension to the analysis in Chapter 5 would be to investigate the link between spontaneous ongoing EEG oscillations and BOLD activity in resting state. Earlier EEG-fMRI resting state studies have mainly focused on the relationship between alpha band activity and the BOLD signal. This is due to relatively high amplitude of the alpha rhythm and its ease of measurement and modulation with experimental conditions. Although results from most of these studies agree on positive correlation between alpha power and the thalamic BOLD response, there is no consensus on the alpha-BOLD relationship in cortical areas (Feige et al. 2005, Moosmann et al. 2003, Laufs et al. 2003a). In particular, different patterns of correlation have been reported across participants. In recent years, efforts have been made to address the discrepancies in the resting state results. Re-evaluation of the existing results as well as recent analysis of new results have demonstrated that extending the frequency range of the oscillatory activity included in the analysis can explain some of the inconsistencies in the results (Mantini et al. 2007, Laufs et al. 2006). Application of PLS-CV method to the spontaneous EEG and fMRI activity in resting state would extend the traditional analysis to include information from multiple frequency bands and electrode channels.

While averaging the data for each participant has the advantage of improved SNR for the PLS-CV analysis, particularly when studying the between participant variability (as in Chapter 5), it may lead to loss of information representing fast fluctuating dynamics of the brain. Another potential extension of the analysis in Chapter 5 is to apply the PLS-CV at the individual participant level and at a finer time scale. Recent evidence suggest that the momentary electric field configurations of the brain, also known as EEG microstates, reflect global functional states of the brain and correlate with the BOLD signal fluctuations during resting state (Britz et al. 2014, Milz et al. 2016, Yuan et al. 2012, Musso et al. 2010). The EEG microstates are defined as short periods (~100ms) during which the EEG scalp topography remains quasi-stable (Britz, Van De Ville & Michel 2010). PLS-CV provides a suitable framework for concurrent analysis of EEG-microstates and the BOLD signal to study the electrophysiological correlates of the resting state networks.
Figure 6.4 illustrates various aspects of the EEG signal that were studied in relationship to the BOLD signal throughout Chapters 3 to 5 of this work. The analysis in Chapter 3 consisted of traditional ERP analysis to extract the event-related phased-lock response. In Chapter 4, using PLS-CV the EEG feature that was studied was the time-locked response or event-related changes in the oscillatory activity. Finally, in Chapter 5, I presented the analysis results for purely oscillatory EEG activity across multiple frequency bands. From another point of view, the EEG data included in the analysis was spatially extended from a limited subset of electrodes to all electrode channels.

These analyses were made possible by improving the EEG data quality (proposed in Chapter 2) as well as addressing methodological issues associated with conventional analysis approaches, through use of the PLS-CV framework. The PLS-CV method enabled a more comprehensive analysis of the data, revealing important information about the underlying dynamics of brain activity. As Laufs describes, “Human EEG activity within a certain frequency band cannot be directly linked to any (mal)function without taking into account its amplitude, spatial distribution, reactivity, intra-and inter-individual variability, and generally speaking the context in which it is observed” (Laufs 2009). The analysis approach used in this work enables symmetric integration of the BOLD signal and EEG oscillations within the “context” by incorporating information from multiple frequency bands and electrode channels in the analysis. Such full spectrum analysis of the EEG data is feasible due to the ability of the PLS-CV technique to deal with high dimensional data sets. Furthermore, within the same model, the scope of the fMRI data matrix can be extended to include whole-brain voxel-wise information.
Figure 6.4: Different approaches to analysis of EEG-BOLD response implemented throughout the chapters. The analysis starts with the conventional time and phase locked ERP analysis and then evolves towards the oscillatory activity of the brain.
Thesis publications

Journal publications

“Comparison of BCG artifact removal methods for evoked response in simultaneous EEG-fMRI”
N.Shams, C.Alain, S.Strother, Journal of neuroscience methods, 2015

“A multivariate approach to analysis of simultaneously recorded evoked EEG and BOLD fMRI sensory responses”, N.Shams, C.Alain, S.Strother (In preparation)

“EEG signatures of vigilance and BOLD response modulation in audiovisual processing”
N.Shams, C.Alain, S.Strother. (In preparation)

Conference submissions

“Simultaneous EEG-fMRI of passive sensory processing” N.Shams, C.Alain, S.Strother. OHBM 2013

“Optimizing EEG artifact removal pipelines in simultaneous EEG-fMRI for passive sensory processing” N.Shams, C.Alain, S.Strother. OHBM 2014

“Simultaneous EEG-fMRI study of BOLD signal variability in the visual cortex” N.Shams, C.Alain, S.Strother. OHBM 2016
References


Babiloni, F., Carducci, F., Cincotti, F., Del Gratta, C., Roberti, G., Romani, G., Rossini, P. & Babiloni, C. 2000, "Integration of high resolution EEG and functional magnetic


acquisition: how far is it from being a standardized technique?", *Magnetic resonance imaging*, vol. 22, no. 10, pp. 1445-1455.


default state of the brain", *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 42, pp. 15236-15240.


Mulert, C.L., Louis. 2010, EEG-fMRI physiological basis, technique, and applications /, Berlin ;Heidelberg : Springer-Verlag, c2010.


Nemenyi, P.B. 1963, Distribution-free multiple comparisons.


Wong, C.W., DeYoung, P.N. & Liu, T.T. 2016, "Differences in the resting-state fMRI global signal amplitude between the eyes open and eyes closed states are related to changes in EEG vigilance", *NeuroImage*, vol. 124, Part A, pp. 24-31.


